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The Installation Restoration Program Toxicology Guide

Volume 3

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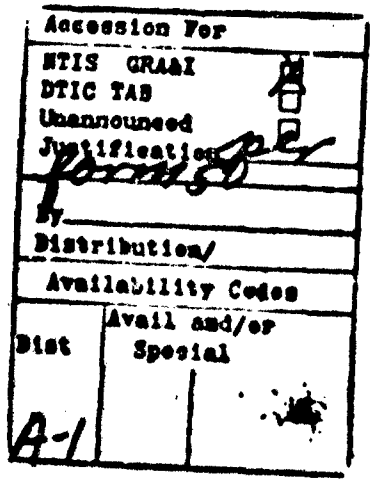
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THE INSTALLATION RESTORATION PROGRAM TOXICOLOGY GUIDE

Volume 3

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Prepared and Published

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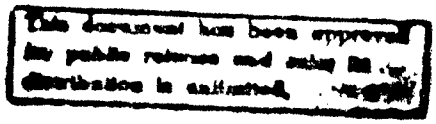
for

Harry G. Armstrong Aerospace Medical Research Laboratory
Aerospace Medical Division
Air Force Systems Command
Wright-Patterson Air Force Base, OH 45433-6573

Under

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PREFACE

One of the objectives of the U.S. Air Force Installation Restoration Program (IRP) is to provide individuals responsible for the management and implementation of the IRP with information to evaluate the health hazards associated with actual or potential contamination of drinking water supplies. The Harry G. Armstrong Aerospace Medical Research Laboratory was requested by HQ USAF/SGPA to develop health and environmental information for each potential contaminant of drinking water supplies associated with USAF installations. This IRP Toxicology Guide consists of four volumes, which were initially issued in 1985-1987. The original Toxicology Guide was produced under contract F33615-81-D-0508 by Arthur D. Little, Inc. for the Biochemical Toxicology Branch, Toxic Hazards Division, Harry G. Armstrong Aerospace Medical Research Laboratory (AAMRL), Wright-Patterson AFB, OH. The updated volumes of the Toxicology Guide include new regulatory requirements and recently published toxicology information. The updated Toxicology Guide was produced under an Interagency Agreement with the U.S. Department of Energy, Oak Ridge National Laboratory (87-TH-0002) for the Hazard Assessment Branch, Toxic Hazards Division, AAMRL, Wright-Patterson AFB, OH.

For each chemical in the IRP Toxicology Guide, the environmental fate, exposure pathways, toxicity, sampling and analytic methods and state and federal regulatory status are outlined. The material provided is intended as an overview of key topic areas; no attempt was made to provide a comprehensive review. Users are encouraged to read the Introduction to Volume 1 of the IRP Toxicology Guide before applying chemical-specific information.

Candidate chemicals for inclusion in subsequent Toxicology Guide updates should be forwarded through MAJCOM bioenvironmental engineers to HQ USAF/SGPA. Consultant service for current toxicological information should be obtained from the USAF OEHL/ECO, Brooks AFB, TX 78235-5000.

Substantial effort was made to assure that the information contained in the Toxicology Guide was current and reliable at the time of publication. Users are encouraged to report apparent discrepancies or errors to AAMRL/THA, Wright-Patterson AFB, OH 45433-6573. Copies of this document are available from: National Technical Information Services, 5285 Port Royal Road, Springfield, VA 22161. Federal Government agencies and their contractors registered with Defense Technical Information Center should direct requests for copies to: Defense Technical Information Center, Cameron Station, Alexandria, VA 22314.

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LIST OF ABBREVIATIONS, ACRONYMS, TERMS AND SYMBOLS

This list of abbreviations, acronyms, terms and symbols is selected from the pages of the Guide. Words and phrases defined here include those occurring in more than one chapter, those indispensable to understanding the material in a chapter and those that may help clarify some of the definitions themselves. Not listed are chemical synonyms which can be found in the chemical index and words adequately defined at the point of use.

A	Acre
AA	Atomic absorption spectroscopy
ACGIH	American Conference of Governmental Industrial Hygienists
Active metals	This refers to metals such as aluminium, calcium, magnesium, potassium, sodium, tin, zinc, and their alloys.
ADI	Acceptable daily intake
ADL	Arthur D. Little, Inc.
Adenocarcinoma	A malignant tumor originating in glandular or ductal epithelium.
Adenoma	A benign growth of glandular tissue.
ae	Acid equivalent
Aerosol	A suspension or dispersion of small solid or liquid particles in air or gas.
AFOSH	Air Force Occupational Safety and Health Standard
Alkali metals	Metals (in Group 1A of the Periodic Table,) such as lithium, sodium, potassium, rubidium, cesium, and francium. The alkali metals react vigorously, at times violently, with water. These metals present a dangerous fire risk when in contact with moisture or oxidizing materials.

Alkaline earth metals	Calcium, barium, strontium, and radium (Group IIA of Periodic Table). Alkaline earth metals are less reactive than sodium and potassium and have higher melting and boiling points.
Ambient water	Surface water
Ambient water criterion	That concentration of a pollutant in a navigable water that, based upon available data, will not result in adverse impact on important aquatic life, or on consumers of such aquatic life, after exposure of that aquatic life for periods of time exceeding 96 hours and continuing at least through one reproductive cycle; and will not result in a significant risk of adverse health effects in a large human population based on available information such as mammalian laboratory toxicity data, epidemiological studies of human occupational exposure data, or any other relevant data.
Amines	A class of organic compounds of nitrogen that may be considered as derived from ammonia (NH_3) by replacing one or more of the hydrogen atoms (H) with straight or branched hydrocarbon (alkyl) groups. All amines are basic in nature and usually combine readily with hydrochloric or other strong acids to form salts.
API	American Petroleum Institute
Aquifer	An underground, permeable saturated strata of rock, sand or gravel containing ground water.
Aromatic	A major group of hydrocarbons containing one or more rings like benzene, which has a six-carbon ring containing three double bonds. Most compounds in this group are derived from petroleum and coal tar and are reactive and chemically versatile. The name characterizes the strong and pleasant odor of most substances of this group. NOTE: The term "aromatic" is often used in perfume and fragrance industries to describe essential oils, which are not aromatic in the chemical sense.
atm	Atmosphere (760 Torr)
ATP	Adenosine triphosphate, a nucleotide cofactor important in many biological reactions where energy is transferred.
Autoignition temperature	The minimum temperature at which the material will ignite without a spark or flame being present. Along with the flash point, autoignition temperature gives an indication of relative flammability.

BCF	Bioconcentration factor, a measure of the cumulative build-up of a specific compound sequentially through a food chain.
Benign	A term meaning noncancerous.
BOD	Biochemical oxygen demand
BUN	Blood urea nitrogen
bw	Body weight
C	Celsius (Centigrade)
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
Calc	A number calculated by Arthur D. Little, Inc.
Carcinogen	Any cancer-producing substance.
Carcinoma	A malignant epithelial tumor.
CAS REG NO	Numeric designation assigned by the American Chemical Society's Chemical Abstract Service which uniquely identifies chemical compound.
cc	Cubic centimeter(s)
CERCLA	Comprehensive Environmental Response Compensation and Liability Act
CFR	Code of Federal Regulations
CL	Ceiling limit value
cm	Centimeter(s) (1E-02 meter)
Chemically active metals	This phrase generally refers to metals such as, calcium, magnesium, potassium, sodium, tin, zinc, and their alloys.

CNS	Central nervous system which consists of the brain and spinal cord. The CNS controls mental activity plus voluntary muscular activity. It also coordinates the parasympathetic and sympathetic nervous systems, which command the body's involuntary functions.
CO	Carbon monoxide
CO_2	Carbon dioxide
Cp	Centipoise
CPSA	Consumer Product Safety Act
C*t	Product of concentration multiplied by time of exposure
CWA	Clean Water Act
d	Density
da	Day(s)
°	Degrees, as in 37°C
DNA	Deoxyribonucleic acid
DOT	U.S. Department of Transportation
Drinking Water	Water which meets the specifications of the water quality standards and is therefore suitable for human consumption and for all usual domestic purposes.
ECD	Electron capture detector
EEC	European Economic Community
EEG	Electroencephalogram, it detects abnormalities in the electrical waves emanating from different areas of the brain.
EKG	Electrocardiogram, a recording of the changes in electrical potential that occur during a cycle of heart muscle activity, producing a characteristic series of waves.
EPA	Environmental Protection Agency
Epithelium	The covering of internal and external surfaces of the body, including the lining of vessels and small cavities.

Epoxide	An organic compound containing a reactive group resulting from the union of an oxygen atom with other atoms (usually carbon) that are joined as shown below: O / \ -C - C- This group, commonly called "epoxy", characterizes the epoxy resins. Epichlorohydrin and ethylene oxide are well-known epoxides.
estim	Estimated value
F	Fahrenheit
FDA	Food and Drug Administration (U.S.A.)
FDCA	Food, Drug and Cosmetic Act
FID	Flame ionization detector
FIFRA	Federal Insecticide, Fungicide and Rodenticide Act
Finished	Tap water, i.e., water that has undergone drinking water treatment
Flammable limits in air	The range of gas or vapor concentrations in air, generally expressed in units percent by volume, capable of supporting combustion when ignited. The lower end of the range is commonly referred to as the lower flammable limit (LFL) and sometimes as the lower explosive limit (LEL). The upper end of the range is called the upper flammable limit (UFL) or the upper explosive limit (UEL).
f_{oc}	Fraction organic carbon in soil ($0 \leq f_{oc} \leq 1$)
FR	Federal Register
ft	Foot
g	Gram(s)
Gavage	Forced feeding through a tube passed into the stomach.
GC	Gas chromatography

GI	Gastro-intestinal
Ground water	Subsurface water that occurs beneath the water table in soils and geologic forms that are fully saturated.
H	Henry's law constant (atm · m^3/mol)
^3H	Chemical symbol for the radioactive isotope of hydrogen of atomic mass 3.
ha	Hectare, a unit of area equal to 10,000 square meters.
HA	EPA's Health Advisory (formerly termed SNARL), an estimate of the no adverse response level for short and long-term exposures to a chemical via drinking water.
Half-life	Time required for removal or degradation of one-half of the original quantity.
Halogen	One of the electronegative elements of Group VIIA of the Periodic Table: fluorine, chlorine, bromine, iodine, and astatine. Fluorine is the most active of all chemical elements.
Halogenated	Containing one or more atoms of halogens.
Hemangioma	A tumor composed of blood vessels.
Hemangiosarcoma	A malignant tumor composed of endothelial cells which line the heart and vessels of the circulatory system.
Hg	Mercury
HMTA	Hazardous Materials Transportation Act
HPLC	High-pressure liquid chromatography
hr	Hour(s)
HSDB	Hazardous Substances Data Bank
Hydrocarbon	An organic compound (as acetylene or benzene) consisting exclusively of the elements carbon and hydrogen and often occurring in petroleum, natural gas, coal, and bitumens.

Hydrolysis	The addition of the hydrogen and hydroxyl ions of water to a molecule, with its consequent splitting into 2 or more simpler molecules.
IARC	International Agency for Research on Cancer
IDLH	Immediately dangerous to life or health concentration; represents the maximum level from which one could escape within 30 minutes without any escape-impairing symptoms or any irreversible health effects.
im	Intramuscular
in	Inch
intradermal	Situated or applied within the skin
in vitro	Describes biological experiments in laboratory apparatus rather than in a living organism.
in vivo	Describes process that occurs within a living organism.
ip	Intraperitoneal
IR	Infrared spectroscopy
IRP	Installation Restoration Program
IU	International units
iv	Intravenous
K_d (or K_p)	Soil sorption coefficient
kg	kilogram(s) (1E+03 grams)
K_{oc}	Soil absorption coefficient normalized to represent amount sorbed per unit weight of organic carbon in soil.
L	Liter(s)
lb	Pound(s)
LC_{50}	The concentration required to kill 50% of test individuals.
LC_{Lo}	Lowest reported lethal concentration.

$LC^{*}t_{50}$	Product of the concentration times time which causes lethality in 50% of the exposed population.
LD_{50}	The dose required to kill 50% of test individuals.
LD_{Lo}	Lowest reported lethal dose.
Lesion	An abnormal change in an organ because of injury or disease.
log K_{ow}	Log of the octanol-water partition coefficient.
Lower flammable limit	The lowest concentration of the material in air which will support combustion.
m	Meter
m^3	Cubic meter(s)
MAC	Maximum allowable concentration
Malignant	Pertaining to the growth and proliferation of certain tumors which terminate in death if not checked by treatment.
MCL	Maximum contaminant level
MDL	Minimum detection limit(s)
mEq	Milliequivalent (1/1000 of an equivalent)
mg	Milligram(s) (10E-3 gram)
mg%	The concentration of a solution expressed in milligrams per 100 mL.
min	Minute(s)
Mineral acids (non-oxiding)	Examples include boric, disulfuric, fluosilicic, hydriodic, hydrobromic, hydrochloric, hydrocyanic, hyfluoric, permonosulfuric, phosphoric, and selenous acids as well as chlorosulfonic acid and various fluorophosphoric acids.
Mineral acids (oxidizing)	Examples include bromic, chloric, chromic, acids hypochlorous, nitric, nitrohydrochloric, perbromic, perchloric, perchlorous, periodic, and sulfuric acids as well as oleum.

mL	Milliliter (1E-03 liter)
MLD	Minimum lethal dose
mm	Millimeter(s) (1E-03 meter)
mM	Millimoles
mol	Gram mole
MPRSA	Marine Protection Research and Sanctuaries Act
MS	Mass spectrometry
Mutagen	A material that induces genetic damage.
MW	Molecular weight
n	Normal (isomer), as in n-butyl.
N	Normal (equivalents per liter, as applied to concentration); nitrogen (as in N-methylpyridine).
Narcosis	A state of stupor, unconsciousness or arrested activity.
NCI	National Cancer Institute
NEPA	National Environmental Policy Act
NFPA	National Fire Protection Association
NIOSH	The National Institute for Occupational Safety and Health
NIOSH No.	A unique, nine-position accession number assigned to each substance listed in the Registry of Toxic Effects of Chemical Substances published by NIOSH.
NIPDWR	National interim primary drinking water regulation
Nitride	Compounds of nitrogen with $N^{\equiv}$ as the anion. These compounds may react with moisture to evolve flammable ammonia gas.
NOEL/NOAEL	No observed (adverse) effect level
NPL	National Priority List
NTP	National Toxicology Program

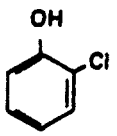
ng	Nanogram(s) (1E-09 gram)
OHM/TADS	Oil and Hazardous Materials Technical Assistance Data System
OSHA	Occupational Safety and Health Act (or Administration)
Oxidation	Any process involving the addition of oxygen, loss of hydrogen, or loss of electrons from a compound.
Oxidizing materials	Any compound that spontaneously evolves oxygen either at room temperature or under slight heating. The term include such chemicals as peroxides, chlorates, perchlorates, nitrates, and permanganates. These can react vigorously at ambient temperatures when stored near or in contact with reducing materials such as cellulosic (i.e., cotton, paper, rayon) and other organic compounds. In general, storage areas for oxidizing materials should be well ventilated and kept as cool as possible.
PEL	Permissible exposure limit, as found in 29CFR 1910.1000.
Percutaneous	Penetration of the skin
pg	picogram(s) (1E-12 grams)
pH	A measure of acidity or alkalinity of a solution on a scale of 0-14; log of the reciprocal of the hydrogen ion concentration.
PID	Photo ionization detector
Pk	Peak concentration.
Plasma	The straw-colored, fluid portion of blood that remains when all cells are removed.
po	By mouth
Polymerizable material	A substance capable of self-polymerization under appropriate conditions. Polymerization reactions are often violent, exothermic, and capable of causing violent rupture of sealed containers.

Polymerization	A chemical reaction, usually carried out with a catalyst, heat, or light, and often under high pressure. In this reaction, a large number of relatively simple molecules combine to form a chain-like macromolecule. This reaction can occur with the release of heat. In a container, the heat associated with polymerization may cause the substance to expand and/or release gas and cause the container to rupture, sometimes violently. The polymerization reaction occurs spontaneously in nature; industrially it is performed by subjecting unsaturated or otherwise reactive substances to conditions that will bring about the combination.
POTWs	Publicly owned treatment works
ppb	Part(s) per billion
ppm	Part(s) per million
ppt	Part(s) per thousand
PVA	Polyvinyl acetate
PVC	Polyvinyl chloride
Raw	Applied to water or waste water that has undergone no treatment.
RCRA	Resource Conservation and Recovery Act
Reactivity (chemical)	Relating to the potential for a substance to undergo chemical transformation or change in the presence of other materials. Such chemical reactions often (but not always) are hazardous and involve evolution of heat, toxic or flammable gases, fires, or expolsions. The products formed by the reaction may have properties or hazards different from those of the chemical reactants.
RBC	Red blood cells

Reducing agents	These agents act to extract and liberate hydrogen from organic substances and may generate toxic and/or flammable gases and heat in contact with water. Many reducing agents may be pyrophoric and may ignite combustible materials in the presence of air. Contact with oxidizing materials may result in violent or explosive reactions. Examples of reducing agents include calcium, phosphorus, sodium, hydrazine, arsine, and metallic acetylides, aluminates, boranes, bromides, carbides, chlorides, hydrides, hydroborates, hyposulfites, iodides, phosphides, selenides, and silanes, as well as metal alkyls such as triethyl aluminum and diethyl zinc.
Reduction	Decreasing the oxygen content or increasing the proportion of hydrogen in a chemical compound or adding an electron to an atom or ion.
REL	Recommended exposure limit
Rf	Retardation factor, i.e., the ratio of the velocity of the interstitial water to the velocity of a pollutant in soil.
RfD	Reference dose
RMCL	Recommended maximum contaminant level
RNA	Ribonucleic acid
RQ	Reportable quantities
SAE	Society of Automotive Engineers
sc	Subcutaneous, beneath the skin
SD	Standard deviation, a measure of the spread of individual measurements of a normally distributed variable.
SDWA	Safe Drinking Water Act
sec	Second(s)
Serum	The clean amber fluid that remains after blood has clotted; plasma without any of the substances involved in clotting.
SGOT	Serum glutamic oxalacetic transaminase, an enzyme released into the serum as the result of tissue injury, especially injury to the heart and/or liver.

SGPT	Serum glutamic pyruvic transaminase, an enzyme released into the serum as a result of tissue injury, especially damage to liver cells.
SH	Sulfhydryl group
SNARL	Suggested no adverse response level
STEL	Short-term exposure limit
STP	Standard temperature and pressure
Subcutaneous	Beneath the skin
Surface water	That water contained on the exterior or upper portion of the earth's surface; it does not include ground water.
Sym	Symmetrical
$t_{1/2}$	Half-life
TD_{Lo}	Lowest reported toxic dose
Teratogen	A material that induces nontransmissible changes (birth defects) in the offspring.
TLV®	Threshold limit value; an ACGIH-recommended time-weighted average concentration of a substance to which most workers can be exposed without adverse effect.
TNT	Trinitrotoluene, an explosive used in the munitions industry.
Toxic metals and their compounds	These include antimony, arsenic, barium, beryllium, bismuth, cadmium, chromium, cobalt, copper, indium, lead, manganese, mercury, molybdenum, nickel, osmium, selenium, thallium, thorium, titanium, zinc, and zirconium; compounds containing these metals; and metallic compounds containing arsines, boron, calcium, cesium, magnesium, silver, strontium, tellurium, tin, tungsten, or vanadium, among others.
TSCA	Toxic Substances Control Act
TWA	Time-weighted-average
µg	Microgram(s) (1E-06 gram)
µL	Microliter(s) (1E-06 liter)

uns	Unsymmetrical
Upper flammable limit	The highest concentration of the material in air which will support combustion.
USAF	United States Air Force
USEPA	United States Environmental Protection Agency
Vol.%	The number of milliliters of a substance in 100 milliliters of the medium.
Water quality standard	Legally enforceable provisions of state or Federal law which consist of a designated use or uses for the waters of the United States and water quality criteria for such waters based upon such uses.
WHO	World Health Organization
wk	Week(s)
w/v	Weight per unit volume
w/w	Weight per unit weight
%	Percent
>	Greater than
≥	Greater than or equal to
<	Less than
≤	Less than or equal to
~	Approximately
->	Yields or causes
+	Plus

COMMON SYNONYMS:	CAS REG.NO.: 95-57-8 FORMULA: C_6H_5ClO NIOSH NO: SK2625000 STRUCTURE: 	AIR W/V CONVERSION FACTOR at 25°C 5.26 mg/m³ ≈ 1 ppm; 0.1903 ppm ≈ 1 mg/m³ MOLECULAR WEIGHT: 128.56
2-Chloro-1-hydroxy-benzene 2-Chlorophenol 2-Hydroxychloro-benzene o-Chlorophenol		

REACTIVITY	Phenols such as o-chlorophenol typically evolve heat in reactions with non-oxidizing mineral acids, organic peroxides or organic hydroperoxides; heat and possibly fire with oxidizing mineral acids or other strong oxidizing agents; and heat and flammable gases with alkali or alkaline earth metals, nitrides or strong reducing agents. Reactions with azo or diazo compounds or hydrazines typically evolve heat and usually innocuous gases. Those with isocyanates, epoxides, or polymerizable compounds may evolve heat and initiate violent polymerization reactions, while those with explosive compounds may initiate an explosion (511).

PHYSICO-CHEMICAL DATA	• Physical State: Liquid (at 20°C)	(23)
	• Color: Colorless to yellow brown	(23)
	• Odor: Medicinal	(67)
	• Odor Threshold: 3.600 ppb	(67)
	• Density: 1.2634 g/mL (at 20°C)	(68)
	• Freeze/Melt Point: 9.30°C	(69)
	• Boiling Point: 175.00°C	(69)
	• Flash Point: 63.90°C closed cup	(51,506)
	• Flammable Limits: No data	
	• Autoignition Temp.: No data	
	• Vapor Pressure: 2.20E+00 mm Hg (at 20°C)	(901)
	• Satd. Conc. in Air: 1.6600E+04 mg/m³ (at 20 °C)	(901)
	• Solubility in Water: 2.85E+04 mg/L (at 20°C)	(67)
	• Viscosity: 4.110 cp (at 25°C)	(68)

PHYSICO-CHEMICAL DATA (Cont.)	• Surface Tension: 4.2250E+01 dyne/cm (at 12.7°C) (68) • Log (Octanol-Water Partition Coeff.): 2.15 (29) • Soil Adsorp. Coeff.: 6.80E+01 (652) • Henry's Law Const.: 1.80E-05 atm · m^3/mol, (estim) (at 25°C) (964) • Bioconc. Factor: 6.80E+00 (estim), 2.14E+02 (bluegill) (659,907)
PERSISTENCE IN THE SOIL-WATER SYSTEM	Relatively mobile in soil-water systems. Volatilization probably important for near-surface soils. Resistant to hydrolysis but fairly easily degraded by photo-oxidation, free-radical oxidation (speculative), and biodegradation.
PATHWAYS OF EXPOSURE	The primary pathway of concern from soil-water system is the migration of o-chlorophenol in groundwater drinking water supplies. Inhalation may also be important in some situations. Ingestion of fish or domestic animals is not likely to be important due to the low potential for bioaccumulation.
HEALTH HAZARD DATA	Signs and Symptoms of Short-term Human Exposure: (972) Ortho-chlorophenol is harmful if swallowed, inhaled or absorbed through skin. Symptoms of exposure may include coughing, wheezing, shortness of breath, laryngitis, headache, nausea and vomiting. Acute Toxicity Studies: ORAL: LD_{50} 670 mg/kg Rat (59) LD_{50} 345 mg/kg Mouse (3504) LD_{50} 670 mg/kg Mouse (3504)

HEALTH HAZARD DATA	Long-Term Effects: No data Pregnancy/Neonate Data: Embryotoxic in rats at high doses Genotoxicity Data: Limited evidence of mutagenic potential Carcinogenicity Classification: IARC - No data NTP - No data EPA - No data

HANDLING PRECAUTIONS (52, 54)	Handle chemical only with adequate ventilation • There are no formal guidelines available for this chemical with respect to respirator use. A self-contained breathing apparatus is recommended • Chemical goggles if there is probability of eye contact • Protective clothing to prevent repeated or prolonged skin contact.

ENVIRONMENTAL AND OCCUPATIONAL STANDARDS AND CRITERIA

AIR EXPOSURE LIMITS:

Standards
- OSHA TWA (8-hr): None established
- AFOSH PEL (8-hr TWA): None established

Criteria
- NIOSH IDLH (30-min): None established
- ACGIH TLV® (8-hr TWA): None established
- ACGIH STEL (15-min): None established

WATER EXPOSURE LIMITS:

Drinking Water Standards
None established

EPA Health Advisories and Cancer Risk Levels
None established

WHO Drinking Water Guideline
No information available.

ENVIRONMENTAL AND OCCUPATIONAL STANDARDS AND CRITERIA (Cont.)

EPA Ambient Water Quality Criteria

- Human Health (3770)
  - Based on ingestion of contaminated water and aquatic organisms, no criterion established due to insufficient data.
  - Based on organoleptic data for controlling undesirable taste and odor quality, the estimated level is 0.1 μg/L.

- Aquatic Life (3770)
  - Freshwater species
    acute toxicity:
    no criterion, but lowest effect level occurs at 4380 μg/L.

    chronic toxicity:
    no criterion, but impairment of fish flavor occurs at concentrations as low as 2000 μg/L.

  - Saltwater species
    acute toxicity:
    no criterion established due to insufficient data.

    chronic toxicity:
    no criterion established due to insufficient data.

REFERENCE DOSES:
ORAL: 5.000E+00 μg/kg/day (3744)

REGULATORY STATUS (as of 01-MAR-89)

Promulgated Regulations

- Federal Programs

Clean Water Act (CWA)

o-Chlorophenol is listed as a toxic pollutant, subject to general pretreatment regulations for new and existing sources, and effluent standards and guidelines (351, 3763). Effluent limitations exist for o-chlorophenol in the following point source categories: electroplating (3767), organic chemicals, plastics, and synthetic fibers (3777), steam electric power generating (3802), and metal finishing (3768). Effluent limitations for phenolic compounds exist in the following point source categories: textile mills (899), petroleum refining (896), iron and steel manufacturing (354), nonferrous metals (894), ferroalloys (895), metal molding and casting (892), and timber products (899). Limitations vary depending on the type of plant and industry.

Safe Drinking Water Act (SDWA)

In states with an approved Underground Injection Control program, a permit is required for the injection of o-chlorophenol-containing wastes designated as hazardous under RCRA (295).

Resource Conservation and Recovery Act (RCRA)

o-Chlorophenol is identified as a toxic hazardous waste (U048) and listed as a hazardous waste constituent (3783, 3784). Waste streams from the following industries contain o-chlorophenol and are listed as specific sources of hazardous wastes: wood preservation (creosote and/or pentachlorophenol preserving processes) and coking (operational residues) (3774, 3765). o-Chlorophenol is subject to land disposal restrictions when its concentration as a hazardous constituent of certain wastewaters exceeds designated levels (3785). o-Chlorophenol is included on EPA's ground-water monitoring list. EPA requires that all hazardous waste treatment, storage, and disposal facilities monitor their ground-water for chemicals on this list when suspected contamination is first detected and annually thereafter (3775). Effective July 8, 1987, the land disposal of hazardous wastes containing halogenated organic compounds in total concentrations greater than or equal to 1000 mg/kg is prohibited. Effective August 8, 1988, the underground injection of these wastes into deep wells is prohibited. Certain variances exist until May, 1990 for land and injection well disposal of some wastewaters and nonwastewaters for which Best Demonstrated Available Technology (BDAT) treatment standards have not been promulgated by EPA (3786). EPA requires that non-liquid hazardous wastes containing halogenated organic compounds (HOCs) in total concentrations greater than or equal to 1000 mg/kg or liquid hazardous wastes containing HOCs in total concentrations greater than or equal to 1% HOCs must be incinerated in accordance with the requirements of 40CFR264.343 or 265.343 (3782).

Toxic Substances Control Act (TSCA)
EPA requires that manufacturers and importers of chemical substances made from 0-chlorophenol submit production, use, exposure and disposal data in order to determine whether there is further need for dioxin and furan testing of the chemical products for which o-chlorophenol is a precursor (3780).

Comprehensive Environmental Response Compensation and Liability Act (CERCLA)
o-Chlorophenol is designated a hazardous substance under CERCLA. It has a reportable quantity (RQ) limit of 45.4 kg. Reportable quantities have also been issued for RCRA hazardous waste streams containing o-chlorophenol but these depend upon the concentrations of the chemicals in the waste stream (3766).

Marine Protection Research and Sanctuaries Act (MPRSA)
Ocean dumping of organohalogen compounds as well as the dumping of known or suspected carcinogens, mutagens or teratogens is prohibited except when they are present as trace contaminants. Permit applicants are exempt from these regulations if they can demonstrate that such chemical constituents are non-toxic and non-bioaccumulative in the marine environment or are rapidly rendered harmless by physical, chemical or biological processes in the sea (309).

Hazardous Materials Transportation Act (HMTA)
The Department of Transportation has designated o-chlorophenol as a hazardous material subject to requirements for packaging, labeling and transportation (3180).

Food, Drug and Cosmetic Act (FDCA)
The level for phenols in bottled drinking water is 0.001 mg/L (365).

- State Water Programs

ALL STATES
All states have adopted EPA Ambient Water Quality Criteria and NPDWRs (see Water Exposure Limits section) as their promulgated state regulations, either by narrative reference or by relisting the specific numeric criteria. These states have promulgated additional or more stringent criteria:

ARIZONA
Arizona has a water quality criterion of 5 µg/L for phenolics in all public waters (3827).

DISTRICT OF COLUMBIA
The District of Columbia has a human health criterion of 0.1 µg/L for o-chlorophenol in public water supply (class D) surface waters and 100 µg/L for class C surface waters (3828, 3827). They also have specific criteria for chlorinated phenols: 3.0 µg/L for class C waters, and 0.04 µg/L for class D (public water supply) waters (3827).

FLORIDA
Florida has water quality criteria for phenolic compounds of 1 μg/L for general use surface waters, and 0.2 mg/L for Class V (navigation, industrial use) surface waters (3220).

ILLINOIS
Illinois has a water quality standard for phenols of 100 μg/L for general use waters, 1 μg/L for Public and Food Processing Water Supplies, and 300 μg/L for Aquatic Life waters (3321, 3827).

INDIANA
Indiana has set the following surface water quality criteria for phenols and phenolic compounds: 10 μg/L for the Ohio River and Wabash River, 300 μg/L (daily maximum) for Lake Michigan and contiguous harbor areas, and 10 μg/L for the Grand Calumet River and Indiana Harbor (3827).

IOWA
Iowa has a surface water quality standard of 50 μg/L for phenolic compounds in Class B and C surface waters (3327). Iowa has also set acute criteria for phenols of 50 μg/L for Class C surface waters, 1000 μg/L for Class B cold surface waters, and 2500 μg/L for Class B warm surface waters, and a chronic criterion of 50 μg/L for all Class B surface waters for the protection of aquatic life (3326).

KANSAS
Kansas has an action level of 0.1 μg/L for o-chlorophenol in groundwater (3213).

KENTUCKY
Kentucky has a surface water quality criterion of 5 μg/L for phenolic compounds in Warm and Coldwater Aquatic Habitats (3827).

LOUISIANA
Louisiana has water quality criteria for phenols of 5 μg/L for drinking water supply waters, 440 μg/L for marine surface waters, and 50 μg/L for fresh surface waters (3406). Louisiana also has a surface water quality criterion of 0.1 μg/L for o-chlorophenol in public water supply waters (3827).

MINNESOTA
Minnesota has a surface water quality criterion of 10 μg/L for phenols in Fisheries and Recreation waters (3827).

MISSISSIPPI
Mississippi requires that the level of phenolic compounds in the public water supply not exceed 1 μg/L (3684). Mississippi also has a surface water quality standard of 50 μg/L for phenolic compounds for fish and wildlife protection (3684).

MISSOURI
Missouri has a water quality criterion of 0.1 μg/L for o-chlorophenol in drinking water (3457).

NEVADA
Nevada has a water quality criterion for phenolics of 1 μg/L for all surface waters (3827).

NEW HAMPSHIRE
New Hampshire has a drinking water standard of 1 μg/L for phenols (3710). New Hampshire also has a surface water quality standard of 1 μg/L for Class A and B waters and 2 μg/L for Class C waters (3684).

NEW JERSEY
New Jersey sets the maximum concentration levels for phenols in the Delaware River and Bay at the following levels: 5 μg/L for Zones 1, 2 and 3, 20 μg/L for Zone 4, and 10 μg/L for Zones 5 and 6. These are maximum levels that apply unless exceeded due to natural conditions (3498).

NEW YORK
New York has set an MCL of 50 μg/L for drinking water and a water quality standard of 1 μg/L for phenol and phenolic compounds in ground-water and surface water classed for drinking water supply (3501).

NORTH CAROLINA
North Carolina has a water quality standard of 1 μg/L for phenolic compounds in Class WS-I, WS-II, and WS-III surface waters (3681).

OHIO
Ohio has a surface water quality standard for phenolic compounds of 1 μg/L for Lake Erie Use waters, Public Water Supply waters, Aquatic Life Habitat Coldwaters and Exceptional Warmwaters, and 10 μg/L for Aquatic Life Habitat Warmwaters (3827).

OKLAHOMA
Oklahoma has set an enforceable Toxic Substance Goal of 0.1 μg/L for o-chlorophenol in public and private water supply surface waters (3534).

OREGON
Oregon has a surface water quality criterion of 1 μg/L for phenols in all surface waters (3827).

PENNSYLVANIA
Pennsylvania has a human health criterion for total phenolics of 5 μg/L measured in surface waters at the point of water supply intake (3561). Pennsylvania also has a human health criterion of 0.1 μg/L for o-chlorophenol in surface water (3561).

RHODE ISLAND
Rhode Island has an acute freshwater quality guideline of 129 μg/L for o-chlorophenol and a chronic guideline of 2.9 μg/L for the protection of aquatic life in surface waters. These guidelines are enforceable under Rhode Island state law (3590).

TENNESSEE
Tennessee sets an effluent limitation of 1.0 mg/L for phenols in effluent from industrial wastewater treatment plants (3827).

VIRGINIA
Virginia has a water quality criterion for phenols of 1 μg/L for groundwater and Public Water Supply surface waters, and a chronic criterion of 1 μg/L for phenol in surface water (3135, 3827).

WEST VIRGINIA
West Virginia sets 0.001 mg/L as the maximum concentration secondary contaminant level for phenols in drinking water in the community public water systems (3576).

WISCONSIN
Wisconsin has set a taste and odor criterion threshold concentration of 0.1 μg/L for o-chlorophenol in surface water (3841).

Proposed Regulations

- Federal Programs

  No proposed regulations are pending.

- State Water Programs

  MOST STATES
  Most states are in the process of revising their water programs and proposing changes in their regulations which will follow EPA's changes when they become final. Contact with the state officer is advised. Changes are projected for 1989-90 (3683).

  WEST VIRGINIA
  West Virginia has proposed a water quality criterion of 5 μg/L for phenolic materials in Public A waters. Final action is expected in late spring 1989 (3835).

EEC Directives

Directive on Drinking Water (533)
The mandatory values for phenols (phenol indices) in surface water treatment categories A1, A2, and A3 used or intended for abstraction of drinking water are 0.001, 0.005, and 0.1 mg/L, respectively. Guideline values for phenols (phenol indices) under treatment categories A2 and A3 are 0.001 and 0.01 mg/L, respectively. No guideline value is given for treatment category A1.

Directive Relating to the Quality of Water for Human Consumption (540)
The maximum admissible concentration for phenols (phenol indices) is 0.5 µg/L. Excluded from this category are natural phenols which do not react to chlorine. No guideline levels for phenols (phenol indices) are given.

Directive on Ground-Water (538)
Direct and indirect discharge into ground-water of substances which have a deleterious effect on the taste and/or odor of ground-water, and compounds liable to cause the formation of such substances in ground-water and to render it unfit for human consumption shall be subject to prior review so as to limit such discharges.

Directive on Bathing Water Quality (534)
Mandatory values for phenols (phenol indices) in bathing water are: (1) no specific odor and (2) concentrations < 0.05 mg/L. Guideline values for phenols (phenol indices) suggest concentrations < 0.005 mg/L.

Directive on Fishing Water Quality (536)
Phenolic compounds in both Salmonid and Cyprinid waters must not be present in such concentrations that they adversely affect fish flavor.

Directive on the Quality Required of Shellfish Waters (537)
The mandatory specifications for organohalogenated substances and metals specify that the concentration of each substance in the shellfish water or in shellfish flesh must not reach or exceed a level which has harmful effects on the shellfish and larvae. The specifications for organohalogenated substances state that the concentation of each substance in shellfish flesh must be so limited that it contributes to the high quality of the shellfish product.

Directive on the Discharge of Dangerous Substances (535)
Organohalogens, organophosphates, petroleum hydrocarbons, carcinogens or substances which have a deleterious effect on the taste and/or odor of human food derived from aquatic environments cannot be discharged into inland surface waters, territorial waters or internal coastal waters without prior authorization from member countries which issue emission standards. A system of zero- emission applies to discharge of these substances into ground-water.

Directive on Marketing and Use of Dangerous Substances (541)
o-Chlorophenol may not be used in ornamental objects intended to produce light or color effects by means of different phases.

Directive on Toxic and Dangerous Wastes (542)
Any installation, establishment, or undertaking which produces, holds and/or disposes of certain toxic and dangerous wastes including phenols and phenol compounds; organic-halogen compounds; chrome compounds; lead compounds; cyanides; ethers and aromatic polycyclic compounds (with carcinogenic effects) shall keep a record of the quantity, nature, physical and chemical characteristics and origin of such waste, and of the methods and sites used for disposing of such waste.

Directive on the Classification, Packaging and Labeling of Dangerous Substances (787)
o-Chlorophenol is classified as a harmful substance and is subject to packaging and labeling regulations.

Directive on Transfrontier Shipment of Hazardous Waste (1433)
When the holder of a hazardous waste such as o-chlorophenol intends to ship it to another member state, authorities of the member states concerned must be provided with information on the source and composition of the waste, measures to be taken to ensure safe transport, insurance against damage and the existence of a contractual agreement with the consignee of the waste. All transfrontier shipments must be properly packed and labeled and must be accompanied by instructions to be followed in the event of danger or accident.

EEC Directives - Proposed
Proposal for a Council Directive on the Dumping of Waste at Sea (1793)
EEC has proposed that the dumping of organohalogen compounds at sea be prohibited.

Resolution on a Revised List of Second-Category Pollutants (545)
o-Chlorophenol is one of the second-category pollutants to be studied by the Commission in the programm of action of the European Communities on Environment in order to reduce pollution and nuisances in the air and water. Risk to human health and the environment, limits of pollutant levels in the environment, and determination of quality standards to be applied will be assessed.

37.1 MAJOR USES

About 99% of the o-chlorophenol produced in the United States is used as a chemical intermediate in the production of higher chlorinated phenols. Other minor uses include their use in the production of specialized phenolic resins, as specialty solvents in the rubber industry, as a polymer intermediate in the manufacture of fire retardant varnishes and as an aminizing agent for cotton fabric (901).

37.2 ENVIRONMENTAL FATE AND EXPOSURE PATHWAYS

37.2.1 Transport in Soil/Ground-water Systems

37.2.1.1 Overview

o-Chlorophenol is expected to be relatively mobile in the soil/ground-water environment when present at low concentrations (dissolved in water) or as a separate organic phase (e.g., resulting from a spill). Transport pathways can be generally assessed by using an equilibrium partitioning model as shown in Table 37-1.

These calculations predict the partitioning of low soil concentrations of o-chlorophenol among soil particles, soil water and soil air. The estimates for the unsaturated topsoil model show that while most of the o-chlorophenol is associated with the stationary soil phase, a significant amount (9.8%) is in the mobile water phase and thus easily leached. Diffusion of o-chlorophenol vapors through the soil-air pores up to the ground surface would appear to be a minor loss pathway based upon the model results. In saturated, deep soils (containing no air and negligible soil organic carbon), a much higher fraction of the o-chlorophenol is likely to be present in the soil water phase (Table 37-1) and available to be transported with flowing ground-water.

o-Chlorophenol is a weak acid (pK_a = 8.52) and thus has a slight tendency to dissociate in water with the loss of a hydrogen ion. In pure water, only 2.9% would be dissociated at pH 7, but 23.2% would be dissociated at pH 8. Thus, in more alkaline waters (pH ≥8) the apparent mobility of o-chlorophenol should be increased since the ionic (dissociated) form would be only weakly sorbed by the stationary soil phase.

37.2.1.2 Soil Sorption on Soils

Based upon its octanol-water partition coefficient of 141, the soil sorption coefficient (K_{oc}) of o-chlorophenol is estimated to be 68. This estimate agrees well with a measured K_{oc} of 51 for a Brookston clay loam at a pH of 5.7 (816), and a second measured value of 75 from a surface soil in Calumet, MI, with a pH of 5.4

TABLE 37-1
EQUILIBRIUM PARTITIONING CALCULATIONS FOR O-CHLOROPHENOL IN MODEL ENVIRONMENTS[a]

Soil Environment	Estimated Percent of Total Mass of Chemical in Each Compartment		
	Soil	Soil-Water	Soil-Air
Unsaturated topsoil at 25°C[b,c]	92.9[e] (90.2)	7.1 (9.8)	1.6E-02 (1.6E-02)
Saturated deep soil[d]	22.2 (21.6)	77.8 (78.4)	- -

a) Calculations based on Mackay's equilibrium partitioning model (34, 35, 36); see Introduction in Volume 1 for description of model and environmental conditions chosen to represent an unsaturated topsoil and saturated deep soil. Calculated percentages should be considered as rough estimates and used only for general guidance.
b) Utilized estimated soil sorption coefficient: K_{oc} = 68.
c) Henry's law constant taken as 1.8E-05 atm · m^3/mol at 25°C (964).
d) Used sorption coefficient K_p = 0.001 K_{oc}.
e) Top number in each entry is for undissociated/fraction of chemical. Bottom number, in parenthesis, is for total chemical concentration and is based upon the assumptions that the pH = 7, and that all of the dissociated fraction is in the soil-water compartment.

(833). However, much higher values of K_{oc} (4,900 to 23,000) have been reported based on studies with lake sediments (818).

As noted above, sorption would be expected to decrease dramatically for pH > 8 because of the chemical's dissociation in this pH range. Sorption will also decrease with decreasing soil organic carbon content.

37.2.1.3 Volatilization from Soils

There are no data providing direct evidence on the importance of volatilization, through the air-filled pores of a soil, as a transport mechanism for o-chlorophenol.

However, comparisons may be made with phenol for which some data are provided in Chapter 36 of this Guide. Those data showed that, given a sufficient time span (weeks to months), volatilization was important for phenol in near-surface soils. Since o-chlorophenol has a vapor pressure about four times that of phenol, and a Henry's law constant about a factor of ten times that of phenol, it may be surmised that volatilization from surface soils will also be an important loss mechanism for o-chlorophenol.

37.2.2 Transformation Processes in Soil/Ground-water Systems

o-Chlorophenol is not likely to be susceptible to hydrolysis, in part because it contains no hydrolyzable functional groups (10, 33, 529). It is probably, like phenol, subject to slow degradation by free radical oxidation. Mabey et al. (33) give estimated oxidation rate constants of <7E+05/M/hr for reaction with singlet oxygen and 1E+7/M/hr for reaction with a peroxy radical. (The same estimates were given for phenol by Mabey et al. (33).) Baker and Mayfield (826) found that o-chlorophenol underwent rapid non-biological degradation in sterile soil. The rate of this degradation increased with temperature and decreased with concentration. In one test in a silica sand/water mixture at 26°C, the o-chlorophenol concentration fell from 100 μg/g of silica to about 15 μg/g after 7 days. These authors speculated that an auto-oxidation mechanism was involved, possibly catalyzed.

A number of studies have shown that o-chlorophenol can be photolytically degraded (10, 806) but only with low wavelength light (below 300 nm) which is of very low intensity in the solar spectrum (10). Because of this, photolysis is not expected to be a significant degradation pathway. When photolysis does occur, reaction products initially formed include pyrocatechol and cyclopentadienic acids (857).

A variety of studies have shown that o-chlorophenol can be biodegraded with reasonable facility (10, 901, 806, 55, 826, 830, 833, 834, 835). Concentrations above 10 mg/L may be toxic and/or inhibitory to degrading microorganisms (806).

The data on biodegradation in soils are somewhat contradictory or confusing. Baker and Mayfield (826), for example, showed o-chlorophenol to be rapidly degraded by microorganisms in aerobically-incubated soil, but not biodegraded in anaerobically incubated soil (both at 23°C). (Non-biological degradation was, however, noted under "anaerobic" conditions, not only at 23°C but also at 4°C [826]). Usipoff et al. (833) found that the chemical was not biodegraded by unacclimated soil cultures (at 20°C) based on data from an electrolytic respirometer (to measure oxygen uptake). However, the CHEMFATE data base (806) provides data from seven other studies on biodegradation in soils or sediments (or using microbes isolated from soils); in all cases, some degradation of o-chlorophenol was noted although the time scales for significant degradation were usually on the order of weeks to a few months.

o-Chlorophenol is easily biodegraded in tests using acclimated seed from sewage treatment plants. Tabak et al. (55), for example, classified the chemical as undergoing significant degradation with rapid adaptation in shake-flask tests.

Based upon the above information, it is concluded that o-chlorophenol can be biodegraded in the natural soil/ground-water environment as long as there are sufficient populations of active microorganisms present. If only low concentrations of microbes are present, biodegradation half-lives might be quite long (months to years).

37.2.3 Primary Routes of Exposure from Soil/Ground-water Systems

The above discussion of fate pathways suggests that o-chlorophenol has a moderate volatility, is weakly adsorbed to soil and has a low potential for bioaccumulation. This compound may volatilize from the soil surface, but that portion not removed by volatilization is likely to be mobile in ground-water. These fate characteristics suggest several potential exposure pathways.

Volatilization of o-chlorophenol from a disposal site could result in inhalation exposures to workers or residents in the area. In addition, the potential for ground-water contamination is high, particularly in sandy soils. It has been detected in ground-water associated with hazardous waste sites, although infrequently. Mitre (83) reported that o-chlorophenol has been found at 3 of the 546 National Priority List (NPL) sites. It was detected at two sites in ground water and in the air at one site. While these data suggest that drinking water exposure from ground-water contamination is possible, it does not appear to be common. The reason for this may be the limited direct uses of this compound which is primarily used as a chemical intermediate (901).

The movement of o-chlorophenol in ground-water may result in discharge to surface waters. Several additional exposure routes may result, including:

- Ingestion exposure resulting from the use of surface waters as drinking water supplies;
- Dermal exposure resulting from the recreational use of surface waters;
- Ingestion exposure resulting from consumption of aquatic organisms that have accumulated o-chlorophenol;
- Ingestion exposure resulting from consumption of meat or poultry that has accumulated o-chlorophenol through dermal contact with or ingestion of surface waters.

In general, exposures to o-chlorophenol associated with surface water contamination from a hazardous waste site can be expected to be lower than exposures from drinking contaminated ground-water. The compound may be

adsorbed or biodegraded before reaching surface water. Some volatilization of o-chlorophenol may occur from surface waters. In addition, the bioaccumulation factor for o-chlorophenol is low, and bioaccumulation in fish or domestic animals would likely be limited.

37.2.4 Other Sources of Human Exposure

Although there is little evidence of exposure of the general population to o-chlorophenol (900, 901), the chemical can be formed as a by-product of water chlorination, thus increasing the risk of exposure (3909). No monitoring data for this compound in drinking water, food or air have been reported (84, 901).

37.3 HUMAN HEALTH CONSIDERATIONS

37.3.1 Animal Studies

37.3.1.1 Carcinogenicity

Experiments designed to determine if o-chlorophenol was a carcinogen, a promotor, or a cocarcinogen, were conducted by Exon and Koller (3909). To test for carcinogenicity, female Sprague-Dawley rats were exposed to 0, 5, 50, or 500 ppm of o-chlorophenol in the drinking water from 3 weeks of age through breeding (at 90 days), parturition and lactation. The progeny (24-32 per group) were weaned at 3 weeks and continued on treatment until tumors appeared or until the experiment was terminated at 24 months. There were no significant differences in tumor latency, incidence, or type in the treated animals compared to the untreated controls.

To test for cocarcinogenicity or promotion, pregnant Sprague-Dawley rats were given the initiator, ethylnitrosourea (ENU) (as the precursor ethylurea in the diet and sodium nitrite in the drinking water), on days 14 to 21 of gestation. The offspring were exposed to o-chlorophenol (5, 50, or 500 ppm) starting either prenatally or postnatally for 24 months. The interpretation of the results of this study was confounded by small sample sizes and an unexpectedly high incidence of tumors in the ENU controls. To compensate for this, the investigators examined tumor incidences and latencies at three different times during the experiment (these corresponded to the time points when the combined tumor incidence in male and female ENU-only treated groups were approximately 25, 50, and 75%). In comparison to the ENU controls, tumor incidence was increased and tumor latency was decreased in all groups of male rats that were treated with ENU and exposed to o-chlorophenol. These results suggest, according to the investigators, that o-chlorophenol is not a complete carcinongen, but that it may act as a cocarcinogen or promotor of carcinogenesis (3909).

Ortho-chlorophenol also exhibited dermal tumor-promoting activities in mice, probably a result of an irritant response. Boutwell and Bosch (902), in a 15-week

experiment, initiated female Sutter mice with a single dermal application of 0.3% dimethylbenzanthracene in benzene. They followed this with twice weekly applications of approximately 25 μL of a 20% o-chlorophenol solution. Ten percent of the treated mice developed epithelial carcinomas and 61% developed papillomas. The promoting activity of o-chlorophenol is probably associated with its irritant effects and subsequent skin hyperplasia and is thus not appropriate for the assessment of human hazard by ingestion.

In a separate study, Boutwell and Bosch (902) treated female Sutter mice with 20% o-chlorophenol in dioxane twice weekly for 12 weeks without prior initiation. At the conclusion of the study, 46% of the survivors had developed papillomas but no epithelial carcinomas were found.

37.3.1.2 Genotoxicity

There is a paucity of short-term test data on o-chlorophenol. Haworth et al. (3276) did not observe a significant increase in histidine revertants in the Salmonella/microsome assay at doses up to 1000 μg per plate with or without metabolic activation.

Chung (903) noted a fivefold increase in chromatid deletions in the bone-marrow cells of Sprague-Dawley rats given oral doses of 130 mg/kg o-chlorophenol every other day for 1 week. After two to three weeks of exposure, complete inhibition of mitosis in bone marrow cells was noted.

V79 Chinese hamster cells treated in culture showed a statistically significant increase in aneuploidy after treatment with o-chloropheonol (3537).

37.3.1.3 Teratogenicity, Embryotoxicity and Reproductive Effects

A study conducted by Exon and Koller in 1982 (904) gave some indication that o-chlorophenol may be feto- or embryotoxic at high doses. They exposed female Sprague-Dawley rats to 0, 5, 50, or 500 ppm o-chlorophenol in drinking water from the 21st day of age through parturition (the rats were bred at 90 days of age). Litter size was significantly decreased in a dose-related manner. Also, the number of stillborn pups born to dams receiving 500 ppm was greater than that seen in controls. These effects were also reported in a later study by the same investigators (3909). Based on the 1982 data, USEPA (3953) identified a no-observed-adverse-effect level (NOAEL) of 50 ppm for the reproductive toxicity of o-chlorophenol.

37.3.1.4 Other Toxicologic Effects

37.3.1.4.1 Short-term Toxicity

Toxicity data on o-chlorophenol are limited. It is considered to be an uncoupler of oxidative phosphorylation (i.e., inhibits production of ATP) and a convulsant

poison (908). In general, the monochlorophenols produce kidney injury with red cell casts in the tubules, fatty infiltration of the liver and hemorrhages in the intestines of rats (12).

o-Chlorophenol is more toxic by the oral than the subcutaneous route. In one study, oral LD_{50} values for both the mouse and rat were 670 mg/kg; a subcutaneous LD_{50} value of 950 mg/kg has been recorded for the rat (47). In a more recent acute toxicity study, oral LD_{50} values for male and female mice were 347 and 345 mg/kg, respectively (3897).

Signs of intoxication in rats are similar whether the compound is administered orally, subcutaneously or intraperitoneally. They include restlessness and increased respiratory rate a few minutes after exposure. A few minutes later, motor weakness develops along with tremors and clonic convulsions which can be induced by noise or touch. Eventually, dyspnea and coma result and continue until death (12).

In rats treated orally every other day for 3 weeks with 65 or 130 mg/kg of o-chlorophenol dissolved in olive oil, weight gain was significantly reduced and liver weight was increased. Liver function was altered as indicated by elevated enzyme levels. Histologically, liver tissue was found to be degenerated (903).

In mice, exposure to 175 mg/kg o-chlorophenol daily by gavage for 14 days resulted in significant body weight reduction and 80% lethality. Mice given 35 or 69 mg/kg/day for the same duration were hyperactive from day 4 onward (858).

No data on dermal exposure are available but since it is lipid soluble and likely to be poorly ionized at physiological pH, absorption by this route is likely (905).

37.3.1.4.2 Chronic Toxicity

Immunologic and hematologic effects were observed in Sprague-Dawley rats treated pre- and post-natally with o-chlorophenol in drinking water. Female Sprague-Dawley rats were supplied with drinking water containing 0, 5, 50, or 500 ppm o-chlorophenol from weaning through breeding (at 90 days), parturition, and lactation. Their three-week-old progeny (12 per group, selected randomly) were placed on o-chlorophenol treatment for an additional 12 to 15 weeks. Humoral and cell-mediated immune responses and macrophage functions were assessed, and body, thymus, spleen, and liver weights were recorded. Of the various immunological parameters tested, the serum antibody response to bovine serum albumin was the only one affected. The response, suppressed at all doses, was not statistically significant. Body and organ weights were not significantly altered. USEPA (3953) identified a no-observed-adverse-effect level (NOAEL) of 500 ppm for the immunotoxicity of phenol, based on this study. Other animals (males and females), treated with 500 ppm of o-chlorophenol for 14 months, exhibited significantly increased red blood cell counts, packed cell volumes, and hemoglobin levels ($p \leq$ or $= 0.05$).

37.3.2 Human and Epidemiologic Studies

There are no data on the effects of o-chlorophenol in humans.

37.3.3 Levels of Concern

A criterion of 0.1 μg/L of o-chlorophenol is recommended by the USEPA based on organoleptic considerations (3770).

Based on the NOAEL of 50 ppm established for reproductive and hematologic effects (904), USEPA (3953) calculated an oral reference dose of 0.005 mg/kg/day (0.35 mg/day for a 70 kg human) for o-chlorophenol. (A reference dose is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan). This study was also used to calculate the composite score (CS), which was used in turn to identify reportable quantity (RQ). The CS derived for o-chlorophenol was 10.4, the RQ, 1000 (3953)

USEPA (3953) evaluated the carcinogenicity study conducted by Exon and Koller (3909) and concluded that because of deficiencies in the study, such as inadequate sample size, the study would not be useful for risk assessment.

37.3.4 Hazard Assessment

The available data on the toxicity of o-chlorophenol are limited. Acute median lethal doses in rodents are in the 670 to 950 mg/kg range. Subchronic studies are few but alteration of liver and immune functions appears to be the principal findings (903, 3909). The induction of chromosomal damage (903) and aneuploidy (3537) by o-chlorophenol have been reported in mammalian somatic tissues. The compound may also be embryotoxic at high doses. There is no information to suggest o-chlorophenol is a direct carcinogen. Some dermal tumor-promoting capability has been demonstrated in mice for o-chlorophenol but it is probably associated with its irritant effects and subsequent skin hyperplasia, and thus, not appropriate for assessment of the systemic hazards associated with o-chlorophenol exposure. The USEPA considers the oral tumor promoting potential of o-chlorophenol, suggested in studies by Exon and Koller (3909) to be tentative because of the high tumor incidence in the ENU controls and the lack of a dose-response relationship (3953). The USEPA concludes that neither the cocarcinogenicity nor the carcinogenicity study is adequate for the assessment of risk to humans, and that the o-chlorophenol should be classified in USEPA Group D (inadequate evidence of carcinogenicity in animals.) Neither IARC (803) nor the NTP (883) have classified this compound according to its carcinogenicity.

37.4 SAMPLING AND ANALYSIS CONSIDERATIONS

Determination of o-chlorophenol concentrations in soil and water requires collection of a representative field sample and laboratory analysis. Soil and water samples are collected in glass containers; extraction of samples should be completed within 7 days of sampling and analysis completed within 30-40 days. In addition to the targeted samples, quality control samples such as field blanks, duplicates, and samples matrices may be specified in the recommended methods.

EPA-approved procedures for the analysis of o-chlorophenol, one of the EPA priority pollutants, in aqueous samples include EPA Methods 604, 625, and 1625 (65), 8040, and 8250 (63). Prior to analysis, samples are extracted with methylene chloride as a solvent using a separatory funnel or a continuous liquid-liquid extractor. Methods 604 and 8040 also provide for a perfluorobenzyl bromide (PFB) derivatization of the sample extract with additional clean-up procedures if interferences are present in the sample matrix. An aliquot of the concentrated sample extract with or without derivatization is injected onto a gas chromatographic (GC) column using a solvent flush technique. The GC column is programmed to separate the semi-volatile organics; o-chlorophenol is then detected with a flame ionization detector (Methods 604 and 8040 without derivatization), as its PFB derivative with an electron capture detector (Methods 604 and 8040 with derivatization) or with a mass spectrometer (Methods 625, 1625, or 8250).

The EPA procedures recommended for o-chlorophenol analysis in soil and waste samples, Methods 8040 and 8250 (63), differ from the aqueous procedures primarily in the preparation of the sample extract. Solid samples are extracted using either soxhlet extraction or sonication methods. Neat and diluted organic liquids may be analyzed by direct injection.

Other methods for the determination of this compound include high performance liquid chromatography with UV absorption (3393) or with fluorescence detection following conversion of the phenolic compound to the dansyl derivative (3162). In the latter case, the derivative is photochemically decomposed by UV irradiation prior to detection to yield a compound with enhanced fluorescence. Capillary GC has been used to separate this compound from other priority pollutants (3356) and a micro-packed column coated with a mixed stationary phase (3427) allows direct determination phenolic pollutants. Gas chromatography coupled with fourier transform infrared spectrometry has also been used (3257).

Typical o-chlorophenol detection limits that can be obtained in waste waters and non-aqueous samples (wastes, soils, etc.) are shown below. The actual detection limit achieved in a given analysis will vary with instrument sensitivity and matrix effects.

Aqueous Detection Limit	Nonaqueous Detection Limit
3.1 µg/L (Method 8040 without derivatization)	2.1 µg/kg (Method 8040 with HD)
0.58 µg/L (Method 604 with derivatization)	0.4 µg/g (Method 8040 with ECD)
33 µg/L (Method 8250)	2.2 µg/g (Method 8250)
10 µg/L (Method 1625)	
0.31 µg/L (Method 604 without derivatization)	
5.8 µg/L (Method 8040 with derivatization)	
3.3 µg/L (Method 625)	

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Note: The nonsequential numbers of the references reflect the order of references as they appear in the master bibliography.

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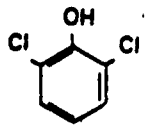
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COMMON SYNONYMS: 2,6-Dichlorophenol	CAS REG.NO.: 87-65-0 FORMULA: $C_6H_4Cl_2O$ NIOSH NO: SK8750000 STRUCTURE: 	AIR W/V CONVERSION FACTOR at 25°C 6.66 mg/m³ ≈ 1 ppm; 0.15 ppm ≈ 1 mg/m³ MOLECULAR WEIGHT: 163.0

REACTIVITY	Dichlorophenols are considered to be both phenols and halogenated organics for compatibility classification purposes. Phenols typically evolve heat in reactions with non-oxidizing mineral acids and organic peroxides or hydroperoxides; heat and possibly fire with oxidizing mineral acids or other strong oxidizing agents; and heat and flammable gases with alkali or alkaline earth metals, nitrides or strong reducing agents. Reactions with azo or diazo compounds or hydrazines typically generate heat and usually innocuous gases. Those with isocyanates, epoxides or polymerizable compounds may evolve heat and initiate violent polymerization reactions, while those with explosive compounds may initiate an explosion. Certain elemental metals and alloys as sheets, rods, drops, etc. may evolve heat and fire in reactions with these compounds, while alkali and alkaline earth metals and certain metals as powders, vapors or sponges may evolve heat and initiate an explosion. Heat evolution and explosion are also possible results of reactions with organic peroxides or hydroperoxides and strong reducing agents (511).

PHYSICO-CHEMICAL DATA	• Physical State: Solid, crystalline (at 20°C)	(54)
	• Color: White	(54)
	• Odor: Strong, penetrating, medicinal	(971)
	• Odor Threshold: 0.003 mg/L	(971)
	• Density: No data	
	• Freeze/Melt Point: 65.00 to 68.00°C	(14)
	• Boiling Point: 218-220°	(14)
	• Flash Point: >100 (by analogy to 2,4 isomer)	(1)
	• Flammable Limits: No data	
	• Autoignition Temp.: No data	

PHYSICO-CHEMICAL DATA (Cont.)	• Vapor Pressure: 3.2E-02 mm Hg (at 20°C) (969) • Satd. Conc. in Air: 2.86E+02 mg/m³ (at 20°C) (1219) • Solubility in Water (mg/L at 25°C): 2300 (967) • Log (Octanol-Water Partition Coeff.): 2.64 (29) • Soil Adsorp. Coeff.: 2.10E+02 (652) • Henry's Law Const.: 3.00E-06 atm · m³/mol (at 25°C) (estim) (964) • Bioconc. Factor: 21 (estim) (659)
PERSISTENCE IN THE SOIL-WATER SYSTEM	Mobile in soil-water systems due, in part, to acid dissociation. Resistant to hydrolysis, but susceptible to free-radical oxidation (speculative). May be susceptible to slow biodegradation; data are contradictory.
PATHWAYS OF EXPOSURE	The primary pathway of concern from soil-water systems is the migration of 2,6-dichlorophenol in groundwater drinking water supplies, although little evidence of such exposure presently exists. Inhalation and the consumption of this compound in fish are not expected to be important exposure pathways.
HEALTH HAZARD DATA	Signs and Symptoms of Short-term Human Exposure: (972) 2,6-Dichlorophenol may be harmful by inhalation, ingestion or skin absorption. It is irritating to the mucous membranes and upper respiratory tract. Prolonged contact can induce severe irritation or burns. Acute Toxicity Studies: (3504) ORAL: LD_{50} 2940 mg/kg Rat LD_{50} 2120 mg/kg Mouse

HEALTH HAZARD DATA	Long-Term Effects: No data Pregnancy/Neonate Data: No data Genotoxicity Data: Limited evidence of mutagenic potential Carcinogenicity Classification: IARC - No data NTP - No data EPA - No data

HANDLING PRECAUTIONS	Handle chemical only with adequate ventilation • There are no formal guidelines available for this chemical with respect to respirator use. A self-contained breathing apparatus is recommended • Chemical goggles if there is probability of eye contact • Natural rubber, neoprene, nitrile, PVC, or PVA protective clothing to prevent repeated or prolonged skin contact.

ENVIRONMENTAL AND OCCUPATIONAL STANDARDS AND CRITERIA

AIR EXPOSURE LIMITS:

Standards
- OSHA PEL (8-hr TWA): None established
- AFOSH PEL (8-hr TWA): None established

Criteria
- NIOSH IDLH (30-min): None established
- ACGIH TLV® (8-hr TWA): None established
- ACGIH STEL (15-min): None established

ENVIRONMENTAL AND OCCUPATIONAL STANDARDS AND CRITERIA (Cont.)

WATER EXPOSURE LIMITS:

Drinking Water Standards
None established

EPA Health Advisories and Cancer Risk Levels
None established

WHO Drinking Water Guideline
No information available.

EPA Ambient Water Quality Criteria

- Human Health (3770)
  - No criterion established due to insufficient data.
    Based on available organoleptic data for controlling undersirable taste and odor, a level of 0.2 μg/L is recommended.

- Aquatic Life (3770)
  - Freshwater species
    acute toxicity:
    no criterion established due to insufficient data.

    chronic toxicity:
    no criterion established due to insufficient data.

  - Saltwater species
    acute toxicity:
    no criterion established due to insufficient data.

    chronic toxicity:
    no criterion established due to insufficient data

REFERENCE DOSES:
No reference dose available.

REGULATORY STATUS (as of 01-MAR-89)

Promulgated Regulations

- Federal Programs

Clean Water Act (CWA)

Chlorinated phenols are listed as a toxic pollutants, subject to general pretreatment regulations for new and existing sources, and effluent standards and guidelines (351, 3763). Effluent limitations exist for effluent containing phenolic compounds in the following point source categories: timber products processing (899), petroleum refining (896), metal molding and casting (892), textile mills (893), iron and steel manufacturing (354), and ferroalloy manufacturing (895). Limitations vary depending on the type of plant and industry.

Safe Drinking Water Act (SDWA)

In states with an approved Underground Injection Control program, a permit is required for the injection of 2,6-dichlorophenol-containing wastes designated as hazardous under RCRA (295).

Resource Conservation and Recovery Act (RCRA)

2,6-Dichlorophenol is identified as a hazardous waste (U082) and listed as a hazardous waste constituent (3783, 3784). Waste streams from the following industries contain 2,6-dichlorophenol and are listed as specific sources of hazardous wastes: pesticides (2,4-D production) and coking (operational residues)(3774, 3765). Effective July 8, 1987, the land disposal of hazardous wastes containing halogenated organic compounds in total concentrations greater than or equal to 1000 mg/kg will be prohibited. Effective August 8, 1988, the underground injection into deep wells of these wastes is prohibited. Certain variances exist until May, 1990 for some wastewaters and contaminated soils for which Best Demonstrated Available Technology (BDAT) treatment standards have not been promulgated by EPA (3786). EPA requires that non-liquid hazardous wastes containing halogenated organic compounds (HOCs) in total concentrations greater than or equal to 1000 mg/kg or liquid hazardous wastes containing HOCs in total concentrations greater than or equal to 1% HOCs must be incinerated in accordance with the requirements of 40CFR264.343 or 265.343 (3782).
2,6-Dichlorophenol is included on EPA's ground-water monitorng list. EPA requires that all hazardous waste treatment, storage, and disposal facilities monitor their ground-water for chemicals on this list when suspected contamination is first detected and annually thereafter (3775).

Toxic Substances Control Act (TSCA)

Under TSCA Section 4 and 8, EPA requires that if manufacture or import of 2,6-dichlorophenol should resume, it must be tested for the presence of dioxins (HDDs) and furans (HDFs) and existing test data must be submitted (3780).

Comprehensive Environmental Response Compensation and Liability Act (CERCLA)
2,6-Dichlorophenol is designated a hazardous substance under CERCLA. It has a reportable quantity (RQ) limit of 45.4 kg. Reportable quantities have also been issued for RCRA hazardous waste streams containing 2,6-dichlorophenol but these depend upon the concentrations of the chemicals in the waste stream (3766).

Marine Protection Research and Sanctuaries Act (MPRSA)
Ocean dumping of organohalogen compounds as well as the dumping of known or suspected carcinogens, mutagens or teratogens is prohibited except when they are present as trace contaminants. Permit applicants are exempt from these regulations if they can demonstrate that such chemical constituents are non-toxic and non-bioaccumulative in the marine environment or are rapidly rendered harmless by physical, chemical or biological processes in the sea (309).

Hazardous Materials Transportation Act (HMTA)
The Department of Transportation has designated 2,6-dichlorophenol as a hazardous material subject to requirements for packaging, labeling and transportation (3180).

Food, Drug and Cosmetic Act (FDCA)
The level for phenols in bottled drinking water is 0.001 mg/L (365).

- State Water Programs

ALL STATES
All states have adopted EPA Ambient Water Quality Criteria and NPDWRs (see Water Exposure Limits section) as their promulgated state regulations, either by narrative reference or by relisting the specific numeric criteria. These states have promulgated additional or more stringent criteria:

ARIZONA
Arizona has a water quality criterion of 5 μg/L for phenolics in all public waters (3827).

DISTRICT OF COLUMBIA
The District of Columbia has a human health criterion of 0.04 μg/L for chlorinated phenols in Class D surface waters and 3.0 μg/L in Class C surface waters (3828).

FLORIDA
Florida has water quality criteria for phenolic compounds of 1 μg/L for general use surface waters, and 0.2 mg/L for Class V (navigation, industrial use) surface waters (3220).

ILLINOIS
Illinois has a water quality standard for phenols of 100 μg/L for general use waters, 1 μg/L for Public and Food Processing Water Supplies, and 300 μg/L for Aquatic Life waters (3321, 3827).

INDIANA
Indiana has set the following surface water quality criteria for phenols and phenolic compounds: 10 µg/L for the Ohio River and Wabash River, 300 µg/L (daily maximum) for Lake Michigan and contiguous harbor areas, and 10 µg/L for the Grand Calumet River and Indiana Harbor (3827).

IOWA
Iowa has a surface water quality standard of 50 µg/L for phenolic compounds in Class B and C surface waters (3327). Iowa has also set acute criteria for phenols of 50 µg/L for Class C surface waters, 1000 µg/L for Class B cold surface waters, and 2500 µg/L for Class B warm surface waters, and a chronic criterion of 50 µg/L for all Class B surface waters for the protection of aquatic life (3326).

KANSAS
Kansas has an action level of 0.2 µg/L for 2,6-dichlorophenol in ground-water (3213).

KENTUCKY
Kentucky has a surface water quality criterion of 5 µg/L for phenolic compounds in Warm and Coldwater Aquatic Habitats (3827).

LOUISIANA
Louisiana has water quality criteria for phenols of 5 µg/L for drinking water supply waters, 440 µg/L for marine surface waters, and 50 µg/L for fresh surface waters (3406). Louisiana also has a surface water quality criterion of 0.2 µg/L for 2,6-dichlorophenol in public water supply waters (3827).

MINNESOTA
Minnesota has surface water quality criterion of 10 µg/L for phenols in Fisheries and Recreation waters (3827).

MISSISSIPPI
Mississippi requires that the level of phenolic compounds in the public water supply not exceed 1 µg/L (3684). Mississippi also has a surface water quality standard of 50 µg/L for phenolic compounds for fish and wildlife protection (3684).

NEVADA
Nevada has a water quality criterion for phenolics of 1 µg/L for all surface waters (3827).

NEW HAMPSHIRE
New Hampshire has a drinking water standard of 1 µg/L for phenols (3710). New Hampshire also has a surface water quality standard of 1 µg/L for Class A and B waters and 2 µg/L for Class C waters (3684).

NEW JERSEY
New Jersey sets the maximum concentration levels for phenols in the Delaware River and Bay at the following levels: 5 μg/L for Zones 1, 2 and 3, 20 μg/L for Zone 4, and 10 μg/L for Zones 5 and 6. These are maximum levels that apply unless exceeded due to natural conditions (3498).

NEW YORK
New York has a surface water quality criterion of 1 μg/L for total chlorinated phenols in class AA, AA-s, A, A-s, B, C, and D surface waters (3827). New York has also set an MCL of 50 μg/L for drinking water and a water quality standard of 1 μg/L for phenol and phenolic compounds in ground-water and surface water classed for drinking water supply (3501).

NORTH CAROLINA
North Carolina has a water quality standard of 1 μg/L for phenolic compounds in Class WS-I, WS-II, and WS-III surface waters (3681).

OHIO
Ohio has a surface water quality standard for phenolic compounds of 1 μg/L for Lake Erie Use waters, Public Water Supply waters, Aquatic Life Habitat Coldwaters and Exceptional Warmwaters, and 10 μg/L for Aquatic Life Habitat Warmwaters (3827).

OKLAHOMA
Oklahoma has set an enforceable Toxic Substance Goal of 0.2 μg/L for 2,6-dichlorophenol in public and private water supply surface waters (3534).

OREGON
Oregon has a surface water quality criterion of 1 μg/L for phenols in all surface waters (3827).

PENNSYLVANIA
Pennsylvania has a human health criterion for total phenolics of 5 μg/L measured in surface waters at the point of water supply intake (3561).

TENNESSEE
Tennessee sets an effluent limitation of 1.0 mg/L for phenols in effluent from industrial wastewater treatment plants (3827).

VIRGINIA
Virginia has a water quality criterion for phenols of 1 μg/L for ground-water and Public Water Supply surface waters, and a chronic criterion of 1 μg/L for phenol in surface water (3135, 3827).

WEST VIRGINIA
West Virginia sets 0.001 mg/L as the maximum concentration secondary contaminant level for phenols in drinking water in the community public water systems (3576).

WISCONSIN
Wisconsin has set a taste and odor criterion threshold concentration of 0.2 μg/L for 2,6-dichlorophenol in surface water (3841).

Proposed Regulations

- Federal Programs

  NONE
  No proposed regulations are pending.

- State Water Programs

  MOST STATES
  Most states are in the process of revising their water programs and proposing changes to their regulations which will EPA's changes when they become final. Contact with state officers is advised. Changes are projected for 1989-90 (3683).

  WEST VIRGINIA
  West Virginia has proposed a water quality criterion of 5 μg/L for phenolic materials in Public A waters. Final action is expected in late spring 1989 (3835).

EEC Directives

Directive on Drinking Water (533)
The mandatory values for phenols (phenol indices) in surface water treatment categories A1, A2 and A3 used or intended for abstraction of drinking water are 0.001, 0.005, and 0.1 mg/L, respectively. Guideline values for phenols (phenol indices) under treatment categories A2 and A3 are 0.001 and 0.01 mg/L, respectively. No guideline value is given for treatment category A1.

Directive Relating to the Quality of Water for Human Consumption (540)
The maximum admissible concentration for phenols (phenol indices) is 0.5 μg/L. Excluded from this category are natural phenols which do not react to chlorine. No guideline levels for phenols (phenol indices) are given.

Directive on Ground-Water (538)
Direct and indirect discharge into ground-water of substances which have a deleterious effect on the taste and/or odor of ground-water, and compounds liable to cause the formation of such substances in ground-water and to render it unfit for human consumption shall be subject to prior review so as to limit such discharges.

Directive on Bathing Water Quality (534)
Mandatory values for phenols (phenol indices) in bathing water are: (1) no specific odor and (2) concentrations ≤0.05 mg/L. Guideline values for phenols (phenol indices) suggest concentrations ≥0.005 mg/L.

Directive on Fishing Water Quality (536)
Phenolic compounds in both salmonid and cyprinid waters must not be present in such concentrations that they adversely affect fish flavor.

Directive on the Quality Required of Shellfish Waters (537)
The mandatory specifications for organohalogenated substances and metals specify that the concentration of each substance in the shellfish water or in shellfish flesh must not reach or exceed a level which has harmful effects on the shellfish and larvae. The specifications for organohalogenated substances state that the concentration of each substance in shellfish flesh must be so limited that it contributes to the high quality of the shellfish product.

Directive on the Discharge of Dangerous Substances (535)
Organohalogens, organophosphates, petroleum hydrocarbons, carcinogens or substances which have a deleterious effect on the taste and/or odor of human food derived from aquatic environments cannot be discharged into inland surface waters, territorial waters or internal coastal waters without prior authorization from member countries which issue emission standards. A system of zero-emission applies to discharge of these substances into ground-water.

Directive on Toxic and Dangerous Wastes (542)
Any installation, establishment, or undertaking which produces, holds and/or disposes of certain toxic and dangerous wastes including phenols and phenol compounds; organic-halogen compounds; chrome compounds; lead compounds; cyanides; ethers and aromatic polycyclic compounds (with carcinogenic effects) shall keep a record of the quantity, nature, physical and chemical characteristics and origin of such waste, and of the methods and sites used for disposing of such waste.

Directive on Transfrontier Shipment of Hazardous Waste (1433)
When the holder of a hazardous waste such as 2,6-dichlorophenol intends to ship it to another member state, authorities of the member states concerned must be provided with information on the source and composition of the waste, measures to be taken to ensure safe transport, insurance against damage and the existence of a contractual agreement with the consignee of the waste. All transfrontier shipments must be properly packed and labeled and must be accompanied by instructions to be followed in the event of danger or accident.

EEC Directives - Proposed
Proposal for a Council Directive on the Dumping of Waste at Sea (1793)
EEC has proposed that the dumping of organohalogen compounds at sea be prohibited.

Resolution on a Revised List of Second-Category Pollutants (545)
2,6-dichlorophenol is one of the second-category pollutants to be studied by the Commission in the programme of action of the European Communities on Environment in order to reduce pollution and nuisances in the air and water. Risk to human health and the environment, limits of pollutant levels in the environment, and determination of quality standards to be applied will be assessed.

38.1 MAJOR USES

The 2,6-isomer of dichlorophenol is used primarily as a feedstock in the manufacture of trichlorophenols, tetrachlorophenols and pentachlorophenol (54).

38.2 ENVIRONMENTAL FATE AND EXPOSURE PATHWAYS

38.2.1 Transport in Soil/Ground-water Systems

38.2.1.1 Overview

2,6-Dichlorophenol is expected to be quite mobile in the soil/ground-water environment when present at low concentrations (dissolved in water). The pure chemical is solid at ambient temperatures (melting point is 65-66°C) and thus bulk quantities (e.g., from a spill) would not be immediately mobile.

2,6-Dichlorophenol is a moderately strong organic acid (reported pK_a values are 6.63 (29) and 6.79 (856)), and thus it has a significant tendency to dissociate in natural waters with the loss of a hydrogen ion. In pure water, the percent dissociation at pH values of 6, 7, and 8 are, respectively, 19%, 70% and 96%. In general, the dissociated form of the chemical (the 2,6-dichlorophenate anion) is more water soluble and less strongly sorbed to soils than the neutral undissociated form.

Transport pathways can be generally assessed by using an equilibrium partitioning model as shown in Table 38-1.

These calculations predict the partitioning of low soil concentrations of the 2,6-dichlorophenol among soil particles, soil water, and soil air. The estimates in this case are given for both the total chemical concentration and for the undissociated fraction. The estimates for the unsaturated topsoil model show that, based on total chemical concentration, most of the chemical (70.7%) is in the mobile water phase and thus easily transported with percolating ground-water. Diffusion of chemical vapors through the soil-air pores up to the ground surface would not appear to be a significant loss pathway based upon the model results. In saturated deep soils (containing no air and negligible soil organic carbon), an even higher fraction of 2,6-dichlorophenol (85.9%) is predicted to be in the soil-water phase and available to be transported with flowing ground-water.

38.2.1.2 Sorption on Soils

Based upon its octanol-water partition coefficient of 436, the soil sorption coefficient (K_{oc}) is estimated to be 210. This is a relatively low number indicative of fairly weak sorption. As noted above, the chemical would be expected to be more

TABLE 38-1
EQUILIBRIUM PARTITIONING CALCULATIONS FOR
2,6-DICHLOROPHENOL IN MODEL ENVIRONMENTS[a]

Soil Environment	Estimated Percent of Total Mass of Chemical in Each Compartment		
	Soil	Soil-Water	Soil-Air
Unsaturated topsoil at 25°C[b,c]	97.6[e] (29.3)	2.4 (70.7)	9E-04 (9E-04)
Saturated deep soil[d]	46.9 (14.1)	53.1 (85.9)	- -

a) Calculations based on Mackay's equilibrium partitioning model (34, 35, 36); see Introduction in Volume 1 for description of model and environmental conditions chosen to represent an unsaturated topsoil and saturated deep soil. Calculated percentages should be considered as rough estimates and used only for general guidance.
b) Utilized estimated soil sorption coefficient: K_{oc} = 210.
c) Henry's law constant taken as 3E-06 atm · m³ /mol at 25°C (964).
d) Used sorption coefficient K_p = 0.001 K_{oc}.
e) Top number in each entry is for undissociated fraction of chemical. Bottom number, in parenthesis, is for total chemical concentration and is based upon the assumptions that the pH = 7 and that all of the dissociated fraction is in the soil-water compartment.

strongly sorbed at lower pH values due to less dissociation of the chemical. No measured sorption data were found in the literature.

38.2.1.3 Volatilization from Soils

The Henry's law constant for 2,6-dichlorophenol (3E-06 atm · m³/mol at 20°C (964)) is approximately the same as that for phenol (7E-06 atm · m³/mol at 20°C (964)). Given that phenol is relatively easily lost from topsoils (see Chapter 36, Section 36.2), it is surmised that 2,6-dichlorophenol would also be relatively easily lost from topsoils. No data are available in the literature to support this conjecture.

38.2.2 Transformation Processes in Soil/Ground-water Systems

2,6-Dichlorophenol is probably not susceptible to degradation by hydrolysis since it has no hydrolyzable functional groups (529).

Baker and Mayfield (826) found that 2,6-dichlorophenol underwent non-biological degradation in sterile soil. In tests at 23°C, 55% of the 2,6-dichlorophenol was decomposed after 40 days in sterile, aerobic (clay loam) soil, while 81% was decomposed after 80 days in sterile, anaerobic soil. The researchers speculated that a radical mechanism, most probably initiated by reactions with molecular oxygen, was involved. A similar phenomenon was noted for other chlorophenols with the degradation rate increasing with temperature and decreasing with chemical concentration.

Baker and Mayfield (826) also reported studies showing 2,6-dichlorophenol to be "rapidly degraded" by microorganisms in aerobically-incubated soil at 23°C. No biodegradation was seen in anaerobically-incubated soil at this temperature. Haider et al. (836) reported the biodegradation of 2,6-dichlorophenol in a para-brown soil (1.26% organic carbon, pH 7.1). Other data reported in the literature provided contradictory information on the biodegradability of this chemical. Boyd and Shelton (834), for example, found no degradation in fresh anaerobic sludge at 37°C.

38.2.3 Primary Routes of Exposure from Soil/Ground-water Systems

The above discussion of fate pathways suggests that 2,6-dichlorophenol has a low volatility, is moderately sorbed to soil, and has a low potential for bioaccumulation. The volatilization of this compound from surface soil is not likely to represent a primary route of exposure. 2,6-Dichlorophenol may be mobile in ground-water, particularly in sandy soils, and may result in drinking water exposure via this route. Exposure pathways involving the accumulation of 2,6-dichlorophenol are likely to be less important than drinking water exposure due to its low bioconcentration factor.

Human exposure as a result of ground-water contamination has not been documented. Mitre (83) did not specifically report the presence of 2,6-dichlorophenol in ground-water associated with any of the 546 National Priority List (NPL) sites. In addition, this compound has not been included in the National surveys of drinking water conducted by EPA (90, 31). However, based on its chemical properties, 2,6-dichlorophenol has some potential to result in drinking water exposure through ground-water contamination. In addition, the movement of this compound in ground-water may result in indirect exposure pathways upon discharge to surface waters. These pathways would include ingestion exposure through the consumption of surface water as a drinking water supply, or dermal exposure through recreational use of surface waters. Bioaccumulation of 2,6-dichlorophenol from surface waters, either by aquatic organisms or domestic animal, are not expected to be dominant exposure pathways due to the low bioconcentration factor for 2,6-dichlorophenol.

38.2.4 Other Sources of Human Exposure

Chlorinated phenols have been found in drinking water as a result of the chlorination of water containing phenol or phenolic compounds (3897). This is a potential source of exposure to 2,6-dichlorophenol for humans. In mice and rats, the organochlorine pesticide hexachlorocyclohexane is metabolized to 2,6-dichlorophenol and other chlorophenols (3925). This suggests that potential exposure to 2,6-dichlorophenol could occur through contact with the pesticide.

38.3 HUMAN HEALTH CONSIDERATIONS

38.3.1 Animal Studies

38.3.1.1 Carcinogenicity

No carcinogenicity data are available for 2,6-dichlorophenol.

38.3.1.2 Genotoxicity

The 2,6-isomer of dichlorophenol was negative for genotoxicity in the Ames test both with and without metabolic activation (970, 3583, 3494, 3276). In addition, Nestmann and Lee (3493) did not observe any effects above control values in two strains of yeast tested for gene conversion or reversion at three loci; no exogenous source of metabolic activation was used in the yeast study.

Chinese hamster V79 cells, in culture with rat hepatocytes or rat fibroblasts as sources of metabolic activation, were treated with 2,6-dichlorophenol and evaluated for forward mutations to 6-thioguanine resistance at the HPRT locus (3275); the incidence of mutants did not exceed negative control levels. In a similar study with V79 cells but without activation, Jansson and Jansson (3335) also observed negative results with concentrations as high as 500 μg/mL. A single report indicated that 2,6-dichlorophenol produced chromosome aberrations in rat bone marrow cells, but details of this Korean study were unavailable for evaluation (54, 9).

38.3.1.3 Teratogenicity, Embryotoxicity and Reproductive Effects

No data are available.

38.3.1.4 Other Toxicologic Effects

38.3.1.4.1 Short-term Toxicity

The toxicity of 2,6-dichlorophenol has not been well studied. It is a severe eye (250 μg/24 hr) and skin (500 mg/24 hr) irritant in rabbits (59). By comparison with

other chlorophenols, it is expected that 2,6-dichlorophenol is absorbed through the skin and from the gastrointestinal tract and rapidly eliminated (971).

In rats, the LD_{50} by the oral route is 2940 mg/kg compared to 390 mg/kg by the intraperitoneal route (59). In male and female CD-1 ICR mice, the oral LD_{50} values are 2198 and 2120 mg/kg, respectively (3897). Chlorinated phenols, in general, cause restlessness and an increased respiratory rate which are followed a few minutes later by motor weakness. Tremors, clonic convulsions, dyspnea and coma set in promptly and continue until death (12). The 2,6-isomer of dichlorophenol produces these signs but the decreased activity and motor weakness do not appear as promptly as they do with other chlorinated phenols (12).

In vitro tests have indicated that 2,6-dichlorophenol (at unspecified levels), inhibits rat liver mitochondrial respiration (971).

38.3.1.4.2 Chronic Toxicity

Administration of 2,6-dichlorophenol to rats at unspecified dosages and routes has been reported to inhibit rat growth, increase the liver to body weight ratio, decrease both the hemoglobin content and hematocrit ratio and to produce hepatic degeneration (59, 71).

38.3.2 Human and Epidemiologic Studies

No human data were found in the literature.

38.3.3 Levels of Concern

The USEPA (3770) has not established an ambient water quality criterion for the protection of human health for 2,6-dichlorophenol due to insufficient data; a criterion of 0.2 $\mu g/L$ is suggested by the USEPA on an organoleptic basis (3770).

38.3.4 Hazard Assessment

The absence of human effects data as well as the lack of carcinogenic, reproductive and long-term animal exposure data for 2,6-dichlorophenol precludes an assessment of the human health hazards associated with exposure to this compound at this time. The compound has been documented to be a severe eye and skin irritant in rabbits (59). A single report indicated induction of chromosomal aberrations in rat marrow cells subsequent to exposure to 2,6-dichlorophenol (54, 59); details of dosing and exposure regimen, however, were not available for evaluation. No genotoxic effects were observed in bacteria, yeast, and mammalian cells in culture (3583, 3494, 3276, 3493, 3335, 3275). The compound has been linked to liver degeneration in rats but again, the dose, route and duration of exposure were unspecified (971).

38.4 SAMPLING AND ANALYSIS CONSIDERATIONS

Determination of 2,5-dichlorophenol concentrations in soil and water requires collection of a representative field sample and laboratory analysis. Soil and water samples are collected in glass containers; extraction of samples should be completed within 7 days of sampling, and analysis completed within 30-40 days. In addition to the targeted samples, quality control samples such as field blanks, duplicates, and fortified sample matrices may be specified in the recommended methods.

2,6-Dichlorophenol is not included among the EPA-designated priority pollutants. However, EPA Methods 604, 625, 1625 (65), 8040 and 8250 (63) would be appropriate methods of choice for the analysis of 2,6-dichlorophenol in aqueous samples. Prior to analysis, samples are extracted with methylene chloride as a solvent using a separatory funnel or a continuous liquid-liquid extractor. Methods 604 and 8040 also provide for a perfluorobenzyl bromide (PFB) derivatization of the sample extract with additional clean-up procedures if interferences are present in the sample matrix. An aliquot of the concentrated sample extract with or without derivatization is injected onto a gas chromatographic (GC) column using a solvent flush technique. The GC column is programmed to separate the semi-volatile organics; 2,6-dichlorophenol is then detected with a flame ionization detector (Methods 604 and 8040 without derivatization), as its PFB derivative with an electron capture detector (Methods 604 and 8040 with derivatization) or with a mass spectrometer (Methods 625, 1625, or 8250).

The EPA procedures recommended for 2,6-dichlorophenol analysis in soil and waste samples, Methods 8040 and 8250 (63), differ from the aqueous procedures primarily in the preparation of the sample extract. Solid samples are extracted using either soxhlet extraction or sonication methods. Neat and diluted organic liquids may be analyzed by direct injection.

2,6-Dichlorophenol detection limits for the various methods were not determined but would be in the range of 0.4-30 μg/L for aqueous samples and 1 μg/g for non-aqueous samples.

Other methods described for the determination of o-chlorophenol may also be appropriate for 2,6-dichlorophenol. This would include high performance liquid chromatography with UV absorption (3393) or with fluorescence detection following conversion of the compound to the dansyl derivative (3162). Differential pulsed polaragraphy has also been investigated for analytical determination of this compound (3864).

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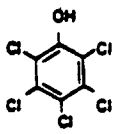
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COMMON SYNONYMS:	CAS REG.NO.: 87-86-5 FORMULA: C_6HCl_5O NIOSH NO: SM6300000 STRUCTURE: 	AIR W/V CONVERSION FACTOR at 25°C (12) 10.88 mg/m³ ≈ 1 ppm; 0.0919 ppm ≈ 1 mg/m³ MOLECULAR WEIGHT: 266.35
Chloropben PCP Penchlorol Penta Pentachlorophenate Pentachlorophenol		

REACTIVITY	Pentachlorophenol may be considered to be both a phenol and halogenated organic for compatibility classification purposes. Phenols typically evolve heat in reactions with nonoxidizing mineral acids, organic peroxides or hydroperoxides; heat and possibly fire with oxidizing mineral acids or other strong oxidizing agents; and heat and flammable gases with alkali or alkaline earth metals, nitrides or strong reducing agents. Reactions with azo or diazo compounds or hydrazines typically generate heat and usually innocuous gases. Those with isocyanates, epoxides, or polymerizable compounds may evolve heat and initiate violent polymerization reactions, while those with explosive compounds may initiate an explosion. Halogenated organic compounds typically generate heat in reactions with cyanides, mercaptans, and other organic sulfides. Those with non-oxidizing mineral acids, amines, and strong oxidizing agents typically evolve heat and toxic gases, while those with caustics or nitrides evolve heat and flammable gases. Reactions with oxidizing mineral acids may generate heat, toxic gases, and fire, while those with azo or diazo compounds or hydrazines may evolve heat and usually innocuous gases. Certain elemental metals and alloys as sheets, rods, drops, etc. may evolve heat and fire in reactions with these compounds, while alkali and alkaline earth metals and certain metals as powders, vapors, or sponges may evolve heat and initiate an explosion. Heat evolution and explosion are also possible results of reactions with organic peroxides and hydroperoxides or strong reducing agents (511).

PHYSICO-CHEMICAL DATA	• Physical State: Solid, crystalline or powder (at 20°C)	(23)
	• Color: White-brown	(23,67)
	• Odor: Phenolic	(3)
	• Odor Threshold: 0.857 to 2.000 mg/L of water	(67)

PHYSICO-CHEMICAL DATA (Cont.)	• Density: 1.9780 g/mL (at 20°C) (3) • Freeze/Melt Point: 190.00°C (23) • Boiling Point: 310.00°C with decomposition (23) • Flash Point: Non-flammable (60) • Flammable Limits: None (60) • Autoignition Temp.: Non-flammable (60) • Vapor Pressure: 1.10E-04 mm Hg (at 20°C) (67) • Satd. Conc. in Air: 1.6000E+00 mg/m^3 (at 20°C) (1219) • Solubility in Water: 1.40E+01 mg/L (at 20°C) (67) • Viscosity: No data • Surface Tension: No data • Log (Octanol-Water Partition Coeff.): 5.12 (29) • Soil Adsorp. Coeff.: 6.35E+04 (for neutral, undissociated molecule) (652) • Henry's Law Const.: 2.80E-06 atm · m^3/mol, (estim) (at 20°C) (964) • Bioconc. Factor: 1.30E+01 (sheepshead minnow), 6.30E+03 (estim) (910,659)
PERSISTENCE IN THE SOIL-WATER SYSTEM	Mobile in soil-water system due largely to acid behavior (formation of phenate anion). Easily photolyzed, resistant to hydrolysis, possibly susceptible to free-radical oxidation, and fairly easily biodegraded, after acclimation, in natural environments.
PATHWAYS OF EXPOSURE	The primary pathway of concern from soil-water systems is the migration of pentachlorophenol in groundwater drinking water supplies, based on its presence at NPL sites and its detection in drinking water surveys. Inhalation exposures are not likely to be important, but consumption of fish or domestic animals may be as a result of bioaccumulation.

HEALTH HAZARD DATA	Signs and Symptoms of Short-term Human Exposure: (38) Pentachlorophenol dust or mist may cause irritation of the eyes and respiratory tract. It readily penetrates skin. Prolonged dermal exposure may cause an acne-like dermatitis. Systemic effects include weakness, loss of appetite, nausea, vomiting, shortness of breath, chest pain, headache, excessive body sweating and dizziness. In fatal cases, body temperature is often extremely high; death generally isdue to cardiac arrest. Acute Toxicity Studies: (3504) INHALATION: LC_{50} 355 mg/m³ Rat LC_{50} 225 mg/m³ Mouse ORAL: LD_{50} 27 mg/kg Rat LD_{50} 117 mg/kg Mouse LD_{50} 168 mg/kg Hamster LD_{Lo} 70 mg/kg Rabbit LD_{Lo} 401 mg/kg Man LD_{Lo} 29 mg/kg Man SKIN: LD_{50} 96 mg/kg Rat LD_{Lo} 40 mg/kg Rabbit Long-Term Effects: Liver and kidney damage Pregnancy/Neonate Data: Embryo- and fetotoxic Genotoxicity Data: Data are conflicting Carcinogenicity Classification: IARC - Group 3 (not classifiable as to its carcinogenicity to humans) NTP - None assigned (studies in progress) EPA - Group D (not classifiable as to human carcinogenicity)

HANDLING PRECAUTIONS (38,52,54,59)	Handle chemical only with adequate ventilation • Vapor concentrations of 0.5-2.5 mg/m³: any supplied-air respirator or self-contained breathing apparatus (if eye irritation occurs, full-facepiece respiratory equipment should be used) • 2.5-25 mg/m³: any supplied-air respirator or self-contained breathing apparatus with full-facepiece • Chemical goggles to avoid eye contact • Natural rubber, neoprene, nitrile, PVC or other protective clothing to prevent prolonged or repeated skin contact with the liquid; no skin surface should be exposed.

ENVIRONMENTAL AND OCCUPATIONAL STANDARDS AND CRITERIA

AIR EXPOSURE LIMITS:

Standards
- OSHA TWA (8-hr): 0.5 mg/m³ (skin)
- AFOSH PEL (8-hr TWA): 0.5 mg/m³ (skin); STEL (15-min): 1.5 mg/m³

Criteria
- NIOSH IDLH (30-min): 150 mg/m³
- ACGIH TLV® (8-hr TWA): 0.5 mg/m³ (skin)
- ACGIH STEL (15-min): Deleted

WATER EXPOSURE LIMITS:

Drinking Water Standards (3883)
MCLG: 200 µg/L (proposed)
MCL : 200 µg/L (proposed)

ENVIRONMENTAL AND OCCUPATIONAL STANDARDS AND CRITERIA (Cont.)

EPA Health Advisories and Cancer Risk Levels (3977)
In the absence of formal drinking water standards, the EPA has developed the following Health Advisories which provide specific advice on the levels of contaminants in drinking water at which adverse health effects would not be anticipated.

- 1-day (child): 1000 µg/L
- 10-day (child): 300 µg/L
- longer-term (child): 300 µg/L
- longer-term (adult): 1000 µg/L
- lifetime (adult): 200 µg/L

WHO Drinking Water Guideline (666)
A health-based guideline for drinking water of 10 µg/L is recommended for pentachlorophenol. A daily per capita consumption of two liters of water was assumed.

EPA Ambient Water Quality Criteria

- Human Health (3770)
  - Based on aquatic organisms and drinking water, 1.01 mg/L. Using available organoleptic data for controlling undesirable taste and odor quality, the estimated level is 30 µg/L. Adjusted for drinking water only, 1.01 mg/L.

- Aquatic Life (3770)
  - Freshwater species
    Freshwater aquatic organisms and their uses should not be affected unacceptably if the 4-day average concentration (in µg/L) of pentachlorophenol does not exceed the numerical value given by e[1.005(pH)-5.290] more than once every 3 years on the average, and if the 1-hour average concentration (in µg/L) does not exceed the numerical value given by e[1.005(pH)-4.830] more than once every 3 years on the average.

  - Saltwater species
    Saltwater aquatic organisms and their uses should not be affected unacceptably if the 4-day average concentration of pentachlorophenol does not exceed 7.9 µg/L more than once every 3 years on the average and if the 1-hour average concentration does not exceed 13 µg/L more than once every 3 years on the average.

REFERENCE DOSES:
ORAL: 3.000E+01 µg/kg/day (3744)

REGULATORY STATUS (as of 01-MAR-89)

Promulgated Regulations

- Federal Programs

Clean Water Act (CWA)

Pentachlorophenol is designated a hazardous substance (347). It is also listed as a toxic pollutant, subject to general pretreatment regulations for new and existing sources, and effluent standards and guidelines (351, 3763). Effluent limitations for pentachlorophenol have been set in the following point source categories: pulp, paper, and paperboard (898), electroplating (3767), steam electric power generating (3802), and metal finishing (3768). Guidelines also exist for effluent containing phenolic compounds in the following point source category: timber products processing (899), petroleum refining (896), metal molding and casting (892), textile mills (893), iron and steel manufacturing (354), and ferroalloy manufacturing (895). Limitations vary depending on the type of plant and industry.

Safe Drinking Water Act (SDWA)

Pentachlorophenol is on the list of 83 contaminants required to be regulated under the SDWA of 1974 as amended in 1986 by January, 1991 (3781). In states with an approved Underground Injection Control program, a permit is required for the injection of pentachlorophenol-containing wastes designated as hazardous under RCRA (295).

Resource Conservation and Recovery Act (RCRA)

Pentachlorophenol is identified as a hazardous waste (U242) and listed as a hazardous waste constituent (3782, 3784). Non-specific sources of pentachlorophenol-containing waste are discarded, unused formulations containing PCP or compounds derived from it, residues resulting from incineration or thermal treatment of soil contaminated with these formulations and wastes from the production or manufacturing use of PCP or of intermediates used to produce its derivatives (325). Waste streams from the following industry contain pentachlorophenol and are listed as specific sources of hazardous wastes: wood preservation (creosote and/or pentachlorophenol preserving processes)(3774, 3765). Effective July 8, 1987, the land disposal of untreated hazardous wastes containing halogenated organic compounds in total concentrations greater than or equal to 1000 mg/kg will be prohibited. Effective August 8, 1988, the underground disposal into deep wells of these wastes is prohibited. Certain variances exist until May, 1990 for some wastewaters and soils for which Best Demonstrated Available Technology (BDAT) treatment standards have not been promulgated by EPA (3786). Pentachlorophenol is on EPA's ground-water monitoring list. EPA requires that all hazardous waste treatment, storage, and disposal facilities monitor their ground-water for chemicals on this list when suspected contamination is first detected and annually

thereafter (3775). EPA requires that non-liquid hazardous wastes containing halogenated organic compounds (HOCs) in total concentrations greater than or equal to 1000 mg/kg or liquid hazardous wastes containing HOCs in total concentrations greater than or equal to 1% HOCs must be incinerated in accordance with the requirements of 40CFR264.343 or 265.343 (3782).

Comprehensive Environmental Response Compensation and Liability Act (CERCLA)
Pentachlorophenol is designated a hazardous substance under CERCLA. It has a reportable quantity (RQ) limit of 4.54 kg. Reportable quantities have also been issued for RCRA hazardous waste streams containing pentachlorophenol but these depend upon the concentrations of the chemicals in the waste stream (3766). Pentachlorophenol has been designated an extremely hazardous substance under SARA Title III Section 313. Any facility at which pentachlorophenol is present in excess of its threshold planning quantity of 10,000 pounds must notify state and local emergency planning officials. If pentachlorophenol is released from the facility in excess of its reportable quantity (RQ), local emergency planning officials must be notified (3766). Under SARA Title III Section 313, manufacturers, processors, importers, and users of pentachlorophenol must report annually to EPA and state officials their releases of this chemical to the environment (3787).

Federal Insecticide, Fungicide and Rodenticide Act (FIFRA)
EPA cancelled the registrations of pesticide products containing pentachlorophenol for non-wood preservative uses (974). For those products with wood preservatives uses, EPA has restricted their use to certified applicators. Manufacturers of wood preservative products are required to make labeling changes and provide consumer information sheets (975).

Marine Protection Research and Sanctuaries Act (MPRSA)
Ocean dumping of organohalogen compounds as well as the dumping of known or suspected carcinogens, mutagens or teratogens is prohibited except when they are present as trace contaminants. Permit applicants are exempt from these regulations if they can demonstrate that such chemical constituents are non-toxic and non-bioaccumulative in the marine environment or are rapidly rendered harmless by physical, chemical or biological processes in the sea (309).

Occupational Safety and Health Act (OSHA)
Employee exposure to pentachlorophenol shall not exceed an 8-hour time-weighted average (TWA) of 0.5 mg/m^3. Employee skin exposure to pentachlorophenol shall be prevented/reduced through the use of protective clothing and practices (3539).

Hazardous Materials Transportation Act (HMTA)
The Department of Transportation has designated pentachlorophenol as a hazardous material with a reportable quantity of 4.54 kg, subject to requirements for packaging, labeling and transportation (3180).

Food, Drug and Cosmetic Act (FDCA)
Pentachlorophenol is approved for use as an indirect food additive as a component of adhesives (3209). The level for phenols in bottled drinking water is 0.001 mg/L (365).

- State Water Programs

ALL STATES
All states have adopted EPA Ambient Water Quality Criteria and NPDWRs (see Water Exposure Limits section) as their promulgated state regulations, either by narrative reference or by relisting the specific numeric criteria. These states have promulgated additional or more stringent criteria:

ARIZONA
Arizona has a water quality criterion of 5 µg/L for phenolics in all public waters (3827).

ARKANSAS
Arkansas' chronic and acute toxicity criteria for pentachlorophenol in surface waters are pH-dependent, and are calculated by the following formulas: chronic toxicity (four day average -µg/L) e[1.005(pH)-5.290], acute toxicity (never to exceed -µg/L) e[1.005(pH)-4.830]. These are for the protection of aquatic life (3587).

DISTRICT OF COLUMBIA
The District of Columbia has a human health criterion of 30 µg/L for pentachlorophenol in public water supply Class D surface waters, and 7 µg/L in Class C waters (3828, 3827).

FLORIDA
Florida has a general surface water criterion of 1 µg/L for chlorinated phenols (includes pentachlorophenol) in all surface waters except Class V. Florida also sets surface water criterion of 0.05 mg/L specifically for pentachlorophenol in Class V waters (naviagation, industry) (3220).

GEORGIA
Georgia sets a criterion concentration of 2.1 µg/L for pentachlorophenol in surface water (3240).

ILLINOIS
Illinois has a water quality standard for phenols of 100 µg/L for general use waters, 1 µg/L for Public and Food Processing Water Supplies, and 300 µg/L for Aquatic Life waters (3321, 3827).

INDIANA
Indiana has set the following surface water quality criteria for phenols and phenolic compounds: 10 μg/L for the Ohio River and Wabash River, 300 μg/L (daily maximum) for Lake Michigan and contiguous harbor areas, and 10 μg/L for the Grand Calumet River and Indiana Harbor (3827).

IOWA
Iowa has a surface water quality standard of 50 μg/L for phenolic compounds in Class B and C surface waters (3327). Iowa has also set acute criteria for phenols of 50 μg/L for Class C surface waters, 1000 μg/L for Class B cold surface waters, and 2500 μg/L for Class B warm surface waters, and a chronic criterion of 50 μg/L for all Class B surface waters for the protection of aquatic life (3326).

KENTUCKY
Kentucky has a surface water quality criterion of 5 μg/L for phenolic compounds in Warm and Coldwater Aquatic Habitats (3827).

LOUISIANA
Louisiana has water quality criteria for phenols of 5 μg/L for drinking water supply waters, 440 μg/L for marine surface waters, and 50 μg/L for fresh surface waters (3406).

MINNESOTA
Minnesota has surface water quality criteria of 10 μg/L for phenols in Fisheries and Recreation waters (3827).

MISSISSIPPI
Mississippi requires that the level of phenolic compounds in the public water supply not exceed 1 μg/L (3684). Mississippi also has a surface water quality standard of 50 μg/L for phenolic compounds for fish and wildlife protection (3684).

MISSOURI
Missouri has set a water quality criterion of 5.3 μg/L at pH 7.0 for pentachlorophenol in drinking water supply waters (3457).

NEVADA
Nevada has a water quality criterion for phenolics of 1 μg/L for all surface waters (3827).

NEW HAMPSHIRE
New Hampshire has a drinking water standard of 1 μg/L for phenols (3710). New Hampshire also has a surface water quality standard of 1 μg/L for Class A and B waters and 2 μg/L for Class C waters (3684).

NEW JERSEY
New Jersey sets the maximum concentration levels for phenols in the Delaware River and Bay at the following levels: 5 µg/L for Zones 1, 2 and 3, 20 µg/L for Zone 4, and 10 µg/L for Zones 5 and 6. These are maximum levels that apply unless exceeded due to natural conditions (3498).

NEW YORK
New York has an MCL of 5 µg/L for pentachlorophenol in drinking water, and a water quality standard of 21 µg/L for ground-waters classed for drinking water supply (3501). New York also has an ambient water quality standard of 0.4 µg/L for pentachlorophenol in Class A, A-s, AA, AA-s, B and C surface waters (3500). In addition, New York has an ambient water quality standard of 1 µg/L for total chlorinated phenols in Class AA, AA-s, A, A-s aquatic surface waters and Class B, C, and D surface waters (3500, 3827).

WISCONSIN
Wisconsin has a human threshold criterion of 0.76 mg/L for pentachlorophenol in public water supply cold surface waters (3842). Wisconsin has also set a taste and odor criterion threshold concentration of 30 µg/L for pentachlorophenol in surface water (3841)

NORTH CAROLINA
North Carolina has a water quality standard of 1 µg/L for phenolic compounds in Class WS-I, WS-II, and WS-III surface waters (3681).

OHIO
Ohio has a surface water quality standard for phenolic compounds of 1 µg/L for Lake Erie Use waters, Public Water Supply waters, Aquatic Life Habitat Coldwaters and Exceptional Warmwaters, and 10 µg/L for Aquatic Life Habitat Warmwaters (3827).

OKLAHOMA
Oklahoma has set a nonenforceable Toxic Substance Goal of 30 µg/L for pentachlorophenol in public and private water supply surface waters. Oklahoma also has a water quality criterion of 1.4 µg/L for pentachlorophenol in fish and wildlife propagation surface waters (3534).

OREGON
Oregon has a surface water quality criterion of 1 µg/L for phenols in all surface waters (3827).

PENNSYLVANIA
Pennsylvania has a human health criterion for total phenolics of 5 µg/L measured in surface waters at the point of water supply intake (3561). Pennsylvania also has a human health criterion of 30 µg/L for pentachlorophenol in surface waters (3561).

RHODE ISLAND
Rhode Island has an acute freshwater quality guideline of 2.2 μg/L for pentachlorophenol and a chronic guideline of 0.05 μg/L for the protection of aquatic life in surface waters. These guidelines are enforceable under Rhode Island state law (3590).

SOUTH DAKOTA
South Dakota requires pentachlorophenol to be nondetectable, using designated test methods, in ground-water (3671).

TENNESSEE
Tennessee sets an effluent limitation of 1.0 mg/L for phenols in effluent from industrial wastewater treatment plants (3827).

VERMONT
Vermont has set a preventive action limit of 110 μg/L and an enforcement standard of 220 μg/L for pentachlorophenol in ground-water (3682).

VIRGINIA
Virginia has a water quality criterion for phenols of 1 μg/L for ground-water and Public Water Supply surface waters, and a chronic criterion of 1 μg/L for phenol in surface water (3135, 3827).

WEST VIRGINIA
West Virginia sets 0.001 mg/L as the maximum concentration secondary contaminant level for phenols in drinking water in the community public water systems (3576).

Proposed Regulations

- Federal Programs

Safe Drinking Water Act (SDWA)
Based on non-oncogenic effects, EPA has proposed a Maximum Contaminant Level Goal (MCLG) and a Maximum Contaminant Level (MCL) of 200 μg/L for pentachlorophenol.

Resource Conservation and Recovery Act (RCRA)
EPA has proposed listing waste streams from the organic pesticides industry (2,4-D production) as specific sources of hazardous waste (3795). EPA has proposed that solid wastes be listed as hazardous in that they exhibit the characteristic defined as EP toxicity when the TCLP extract concentration is equal to or greater than 3.6 mg/L pentachlorophenol. Final promulgation of this Toxicity Characteristic Rule is expected in June, 1989 (1565).

- State Water Programs

MOST STATES

Most states are in the process of revising their water programs and proposing changes to their regulations which will EPA's changes when they become final. Contact with state officers is advised. Changes are projected for 1989-90 (3683).

KANSAS

Kansas has proposed a water quality standard of 220 µg/L for pentachlorophenol in ground-water (3213).

MINNESOTA

Minnesota has proposed a Recommended Allowable Limit (RAL) of 220 µg/L for pentachlorophenol in drinking water (3451). Minnesota has also proposed Sensitive Acute Limits (SAL) of 13.7 µg/L for pentachlorophenol in cold surface waters and 15.7 µg/L for other designated surface waters, in addition to chronic criteria of 4.3 µg/L for cold surface waters and 5 µg/L for other designated surface waters. All values are pH-dependent. Criteria are for the protection of human health (3452).

WEST VIRGINIA

West Virginia has proposed a water quality criterion of 5 µg/L for phenolic materials in Public A waters. Final action is expected in late spring 1989 (3835).

EEC Directives:

Directive on Drinking Water (533)

The mandatory values for phenols (phenol indices) in surface water treatment categories A1, A2 and A3 used or intended for abstraction of drinking water are 0.001, 0.005 and 0.1 mg/L, respectively. Guideline values for phenols (phenol indices) under treatment categories A2 and A3 are 0.001 and 0.01mg/L, respectively. No guideline value is given for treatment category A1.

Directive Relating to the Quality of Water for Human Consumption (540)

The maximum admissible concentration for phenols (phenol indices) is 0.5 mg/L. Excluded from this category are natural phenols which do not react to chlorine. No guideline levels for phenols (phenol indices) are given.

Directive on Ground-Water (538)

Direct and indirect discharge into ground-water of substances which have a deleterious effect on the taste and/or odor of ground-water, and compounds liable to cause the formation of such substances in ground-water and to render it unfit or human consumption shall be subject to prior review so as to limit such discharges.

Directive on Bathing Water Quality (534)
Mandatory values for phenols (phenol indices) in bathing water are: (1) no specific odor and (2) concentrations ≤0.05 mg/L. Guideline values for phenols (phenol indices) suggest concentrations ≤0.005 mg/L.

Directive on Fishing Water Quality (536)
Phenolic compounds in both salmonid and cyprinid waters must not be present in such concentrations that they adversely affect fish flavor.

Directive on the Quality Required of Shellfish Waters (537)
The mandatory specifications for organohalogenated substances and metals specify that the concentration of each substance in the shellfish water or in shellfish flesh must not reach or exceed a level which has harmful effects on the shellfish and larvae. The specifications for organohalogenated substances state that the concentation of each substance in shellfish flesh must be so limited that it contributes to the high quality of the shellfish product.

Directive on the Discharge of Dangerous Substances (535)
Organohalogens, organophosphates, petroleum hydrocarbons, carcinogens or substances which have a deleterious effect on the taste and/or odor of human food derived from aquatic environments cannot be discharged into inland surface waters, territorial waters or internal coastal waters without prior authorization from member countries which issue emission standards. A system of zero- emission applies to discharge of these substances into ground-water.

Directive on Marketing and Use of Dangerous Substances (541)
Pentachlorophenol may not be used in ornamental objects intended to produce light or color effects by means of different phases.

Directive on Toxic and Dangerous Wastes (542)
Any installation, establishment, or undertaking which produces, holds and/or disposes of certain toxic and dangerous wastes including phenols and phenol compounds; organic-halogen compounds; chrome compounds; lead compounds; cyanides; ethers and aromatic polycyclic compounds (with carcinogenic effects) shall keep a record of the quantity, nature, physical and chemical characteristics and origin of such waste, and of the methods and sites used for disposing of such waste.

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Directive on Classification, Packaging and Labeling of Pesticides (786)

Pentachlorophenol is listed as a Class I/a substance and is subject to packaging and labeling regulations.

Directive on the Classification, Packaging and Labeling of Dangerous Substances (787)
Pentachlorophenol is classified as a toxic substance and is subject to packaging and labeling regulations.

Directive on Paints, Varnishes, Printing Inks, Adhesives and Similar Products (1334)
Pentachlorophenol is classified as a toxic substance when present in concentrations greater than 5% and as a harmful substance when present in concentrations ranging from 0.5 to 5%.

Directive on Transfrontier Shipment of Hazardous Waste (1433)
When the holder of a hazardous waste such as pentachlorophenol intends to ship it to other member states, authorities of the member states concerned must be provided with information on the source and composition of the waste, measures to be taken to ensure safe transport, insurance against damage and the existence of a contractual agreement with the consignee of the waste. All transfrontier shipments must be properly packed and labeled and must be accompanied by instructions to be followed in the event of danger or accident.

Directive on Limit Values and Quality Objectives for Discharges of Certain Dangerous Substances (1792)
Pursuant to the Directive on the Discharge of Dangerous Substances, the quality objective for pentachlorophenol is 2 μg/L. The emission standard of pentachlorophenol for the production of sodium pentachlorophenate by hydrolysis of hexachlorobenzene is 1 mg/L water discharged as a monthly average and 2 mg/L water discharged as a daily average. These regulations must be complied with as of January 1, 1988.

EEC Directives - Proposed
Proposal for a Council Directive on the Dumping of Waste at Sea (1793)
EEC has proposed that the dumping of organohalogen compounds at sea be prohibited.

Resolution on a Revised List of Second-Category Pollutants (545)
Pentachlorophenol is one of the second-category pollutants to be studied by the Commission in the programme of action of the European Communities on Environment in order to reduce pollution and nuisances in the air and water. Risk to human health and the environment, limits of pollutant levels in the environment, and determination of quality standards to be applied will be assessed.

39.1 MAJOR USES

Until recently, most of the pentachlorophenol (PCP) produced in the United States was consumed in the wood preserving industry (approximately equal to 90%) where it was used to prevent discoloration, enhance toughness and prevent attack by insects and fungi. About 9% was used in the manufacture of sodium pentachlorophenate. Additional minor applications included its use in the textile, tanning and paint industries (909). EPA has proposed canceling the registrations of pesticide products containing PCP for non-wood preservative (974) and restricting the use of wood preservative applications to certified applicators (975).

Commercial PCP formulations contain from 85% to 99% PCP as well as different chlorophenol impurities (5-10% tetrachlorophenol, 1% trichlorophenol, about 5% chlorinated phenoxyphenols) and minor amounts of highly toxic polychlorinated dibenzo-p-dioxins and dibenzofurans (10-1000s mg/kg) (909).

39.2 ENVIRONMENTAL FATE AND EXPOSURE PATHWAYS

39.2.1 Transport in the Soil/Ground-water Systems

39.2.1.1 Overview

PCP is expected to be relatively mobile in the soil/ground-water environment when present at low concentrations (dissolved in water). The pure chemical is a solid at ambient temperatures (melting point is 190°C) and thus bulk quantities (e.g., from a spill) would not be immediately mobile.

PCP is a moderately strong organic acid (reported pK_a values are 4.5 (856), 4.59 (29) and 4.74 (10)), and thus it is essentially completely dissociated into the phenate anion and hydrogen cation under typical pH conditions. In pure water, the percent dissociation at pH values of 6, 7 and 8 are, respectively, 96.2%, 99.6% and 99.96% based on pK_a = 4.59. PCP would be 50% dissociated when the pH was equal to the pK_a (i.e., at pH 4.6). In general, the dissociated form of the chemical (the phenate anion) is more soluble in water, less strongly sorbed to soils, and less bioaccumulated in biota than the neutral, undisssociated form. The solubility as a function of pH has been given by Branson and Blau (847) as follows:

pH	% Dissociated	Solubility (mg/L)
3	1.8	14
5	64.0	34
6	95.0	75
7	99.5	1,950
8	99.95	19,300

The change in soil sorption with pH has been measured by Choi et al. (48) and does indeed show a dramatic decrease in sorption as the pH goes from 5 to 7 (Figure 39-1). Thus, the importance of pH in the soil/ground-water mobility of PCP is difficult to overstate.

Transport pathways can be generally assessed by using an equilibrium partitioning model as shown in Table 39-1. These calculations predict the partitioning of low soil concentrations of PCP among soil particles, soil water, and soil air. The estimates in this case are given both for the total chemical concentrations and for the undissociated fraction, the latter being only technically valid for very low pH values (e.g., <4). The estimates for the unsaturated topsoil model show that, based on total chemical concentration, essentially all of the chemical (99.6%) is predicted to be in the mobile water phase and thus easily transported with percolating ground water.

Diffusion of the chemical vapors through the soil-air pores and up to the ground surface would not appear to be a significant loss pathway based upon the model results. (Data presented below, however, indicate that both volatilization and sorption are, perhaps, more important than are predicted by this model). In saturated deep soils (containing no air and negligible soil organic carbon), the model predicts the same high proportion of PCP (99.6%) in the mobile aqueous phase if total concentrations of PCP (dissociated + undissociated) are used as the basis.

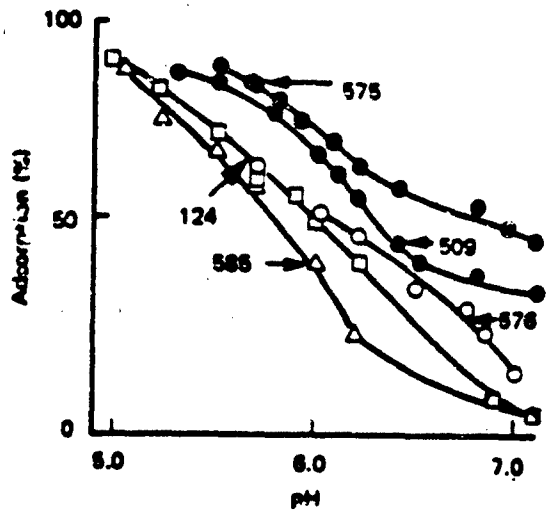
39.2.1.1.2 Experimental Fate and Transport Studies

Numerous laboratory and field studies have been carried out to study the mobility and persistance of PCP under various environmental conditions (807, 810, 826, 835, 837, 838, 839, 840, 841, 842, 843, 844, 845, 846). Although few of these studies focused on fate and transport in just the soil/ground-water environment, all the studies (including those simulating surface waters) provide valuable information on the relative importance of various fate and transport processes under fairly realistic conditions.

The basic findings of the laboratory and field studies cited above provide a reasonably consistent picture of PCP environmental fate and transport. This includes: (1) fairly rapid photodegradation in sunlit surface waters; (2) moderate to weak sorption on soils and sediments (sorption weakest on alkaline and reduced soils); and (3) reasonable susceptibility to biodegradation, at least under aerobic conditions. Some evidence of a non-biological, non-photolytic degradation mechanism is also provided. Some evidence of volatilization is also provided; however, most of the experiments used ^{14}C-labeled PCP and apparent concentrations in air are probably due mostly to $^{14}CO_2$ which would be derived from the biodegradation of ^{14}C-PCP.

Other laboratory ecosystem and field studies of the fate and transport of PCP have been summarized by Callahan (10), Scow and coworkers (909) and the Syracuse Research Corporation (806).

FIGURE 39-1
RELATION OF THE APPARENT ADSORPTION TO THE pH OF THE SUPERNATANT LIQUID (Initial concentration: 100 ppm)



Note: Numbers represent different soil samples

No.	Soil Type
24	Montomorillonitic
509	Humus-rich allophanic
575	Humus-rich aliophanic
576	Allophanic
585	Halloystic

Source: Choi et al. (848)

TABLE 39-1
EQUILIBRIUM PARTITIONING CALCULATIONS FOR
PENTACHLOROPHENOL IN MODEL ENVIRONMENTS[a]

Soil Environment	Estimated Percent of Total Mass of Chemical in Each Compartment		
	Soil	Soil-Water	Soil-Air
Unsaturated topsoil at 25°C[b]	99.99[c] (0.4)	8.2E-03 (99.6)	3E-06 (3E-06)
Saturated deep soil[d]	99.6 (0.4)	0.4 (99.6)	- -

a) Calculations based on Mackay's equilibrium partitioning model (34, 35, 36); see Introduction in Volume 1 for description of model and environmental conditions chosen to represent an unsaturated topsoil and saturated deep soil. Calculated percentages should be considered as rough estimates and used only for general guidance.
b) Utilized estimated soil sorption coefficient: K_{oc} = 63,500. (Valid only for neutral molecule.)
c) Henry's law constant taken as 2.8E-06 atm · m³/mol at 20°C (964).
d) Used sorption coefficient $K_p = 0.001\ K_{oc}$.
e) Top number in each entry is for undissociated fraction of chemical. Bottom number, in parenthesis, is for total chemical concentration and is based upon the assumptions that the pH = 7 and that all of the dissociated fraction is in the soil-water compartment.

39.2.1.2 Sorption on Soils

No accurate prediction can be made of the soil sorption coefficient (K_{oc}) from the octanol-water partition coefficient (K_{ow}) of PCP because of the strong dissociation of PCP, and the uncertain effect of pH on the value of K_{ow} and the K_{ow}-K_{oc} correlation. As noted above, soil sorption of PCP is generally weak, but does become significant at lower pH values as shown by the data in Figure 39-1.

The data of Choi and Aomine (848) do show some increased sorption with increasing soil organic matter as would be expected. Other data show that PCP is somewhat more strongly sorbed to oxidized sediments than to reduced sediments (845, 846). The soil sorption constant calculated from the data of DeLaune et al. (845) is K_{oc} = 2900 (reduced sediment, pH 6.8) and K_{oc} = 4200 (oxidized sediment, pH 6.8).

39.2.1. Volatilization from Soils

Based upon the relatively low vapor pressure of PCP (10E-04 mm Hg 20°C) and low value of Henry's law constant (2.8E-06 atm · m^3/mol at 20°C), volatilization from soils would not be expected to be an important loss pathway. However, some of the laboratory and field studies cited in Section 39.2.1.1.2 had PCP losses which were attributed to volatilization (838, 839, 842, 843). Other ecosystem studies also show significant air concentrations (806). (See especially the studies by Kilzer et al. (849), Gile and Gillett (850), and Metcalf et al. (851)). Any such volatilization would only be important for surface soils.

39.2.2 Transformation Processes in Soil/Ground-water Systems

The ease of photolytic degradation in sunlit surface waters was mentioned above and is documented by several laboratory and field studies (838, 840, 841, 844, 852) and by other studies (10, 909, 806). Initial photochemical reactions commonly involve the loss of a chlorine or the substitution of a hydroxy group for a chlorine.

PCP is probably not susceptible to hydrolysis since it has no hydrolyzable functional groups (529).

The possibility of degradation by some other non-biological process is raised by the studies of Baker and Mayfield (826) and Baker et al. (835) where some degradation was seen, over time scales of 1 to 6 months, in test systems using sterile soils. A free-radical oxidation mechanism may be involved.

A fairly large body of data from studies on the biodegradability of PCP is available (10, 909, 806, 853, 854, 855, 826, 839, 842). The conclusions from these studies span a wide range, all the way from "no degradation" after 40 days in a stream water die-away test to "significant degradation with gradual adaptation" in a shake-flask static incubation test with municipal sewage seed. The weight of evidence does show, however, that PCP is moderately easily biodegraded in the natural environment, including aerobic soils (but probably not anaerobic soils).

Numerous factors will affect the rate at which PCP biodegrades including temperature, soil composition (especially concentration of organic carbon and nutrients, and pH), redox potential, microorganism population and PCP concentration. Valo et al. (854), for example, found no PCP degradation below 8°C or above 50°C in small-scale trickling filter tests; they also found the optimum pH for biodegradation in their system to be from 6.4 to 7.2, and that while PCP degradation continued when the partial pressure of oxygen (pO_2) was lowered to 0.0002 atm, the degradation ceased when pO_2 was further decreased to 0.00002 atm. Concentrations of PCP above 0.2 mg/L may inhibit biodegradation. Under optimum conditions, biodegradation half-lives may be on the order of just a few days; under less than optimum conditions, the half-lives may extend to weeks or months; under poor conditions it could be months to many years. Finally, it is worth noting that PCP

undergoes ultimate (complete) biodegradation in which all carbon is converted to CO_2.

39.2.3 Primary Routes of Exposure from Soil/Ground-water Systems

The above discussion of fate pathways suggests that PCP has a low volatility, is strongly sorbed (categorization ignores dissociation, estimated K_{oc} value too high) to soil, and has a moderate potential for bioaccumulation. The volatilization of this compound from surface soil is not likely to represent a primary route of exposure. Although PCP is strongly sorbed to soil, it may be mobile in alkaline and sandy soils with a potential for drinking water exposure through ground-water contamination. Exposure pathways involving the accumulation of PCP by biota may be important due to its moderate bioconcentration factor.

PCP is a relatively common contaminant at hazardous waste disposal sites. Mitre (83) reported that PCP was found at 16 of the 546 National Priority List (NPL) sites. It was detected at 12 sites in ground water, 8 sites in surface water, and at 1 site in the air. These data suggest that both ground-water and surface-water pathways may be important.

Although its properties suggest it can be strongly sorbed to soil, the occurrence of PCP in ground water at NPL sites indicates that drinking water exposure may result from soil/ground-water systems. In addition, surface water contamination may result either from run-off of PCP adsorbed to soil particles, or from the discharge of ground water to surface water. A number of exposure pathways may result from surface water contamination. They are:

- Direct ingestion exposure as a result of the use of surface waters as drinking water supplies;
- Dermal exposure resulting from recreational use of surface waters;
- Ingestion exposure resulting from the consumption of aquatic organisms or domestic animals that have accumulated PCP.

In general, these exposure pathways are not likely to be the primary routes of exposure from a soil/ground-water system because PCP is likely to be photolyzed and/or biodegraded upon reaching surface waters (909). The bioaccumulation of PCP from surface waters, either by aquatic organisms or domestic animals, may be important in some situations due to the moderate bioconcentration factor for PCP.

39.2.4 Other Sources of Human Exposure

PCP is widely distributed in the environment, and there are a number of potential sources of exposure. Exposure through drinking water is prevalent, but exposure levels are low. In the National Organics Monitoring Survey, EPA detected PCP in 86 of 108 water supplies, with a mean of 0.07 μg/L and a maximum of 0.70 μg/L (90).

PCP has also been found in a variety of food products including dairy products, grains and cereals, root vegetables, and sugars and adjuncts. On the basis of available data, FDA estimated an average intake of 0.76 mg/day for a 15-year-old male (884). EPA calculated an average intake of 1.5 mg/day for adults (885). WHO (3961) estimates a lower average daily intake of 10 μg of PCP/person. This estimate is for an average person with no known exposure and includes 6 μg/day from food, 2 μg/day from drinking water, and 2 μg/day from the ambient air (exclusive of exposure to consumer products). In addition to direct food contamination, exposure to compounds that are biotransformed to PCP (hexachlorobenzene and lindane) may add to the body burden of PCP (3961).

The nature of present and past uses of PCP have led to releases to air and inhalation exposures, particularly to workers and persons using these products. As all non-wood uses of PCP are or will be cancelled, inhalation exposure resulting from these will be eliminated (974). In addition, most use of PCP as a wood preservative will be limited to certified applicators (975). PCP will also be restricted from use on logs intended for homes (975), although individuals residing in currently existing log homes will still be exposed to PCP in the home.

Dermal exposure to PCP will also be limited, as consumer of this wood-preserving product will be eliminated (974, 975).

39.3 HUMAN HEALTH CONSIDERATIONS

39.3.1 Animal Studies

39.3.1.1 Carcinogenicity

Innes et al. (911) administered technical PCP by gavage to (C57BL/6xC3H/Anf)F_1 and (C57BL/6xAKR)F_1 mice at doses of 46.4 mg/kg on days 7-28 of age followed by 130 mg/kg in the diet up to 18 months of age. The tumor incidence above control values was not statistically significant. In Sprague-Dawley rats fed up to 30 mg/kg/day purified PCP for 22-24 months, no alteration in tumor incidence or duration of lifespan was noted (919).

However, in an NTP bioassay, there was some evidence of carcinogenic activity for female mice fed diets containing technical-grade PCP. B6C3F$_1$ (50 mice/sex/dose and 35 mice/sex/control group) were given technical grade pentachlorophenol (PCP-T) in the diet at concentrations of 0, 100, or 200 ppm, or a commercial preparation, Dowicide EC-7, at concentrations of 0, 100, 200, or 600 ppm for 2 years (3927). The average potential daily doses were approximately 17-18 or 35 mg/kg for PCP-T, and approximately 17-18, 34-37, or 114-118 mg/kg of EC-7. Survival was not affected by any dose of either of the test chemicals.

The incidences of hepatocellular adenomas or carcinomas combined were increased and were dose-related in both males and females that were exposed to PCP-T (males: control, 22%; low dose, 55%, p=0.003 by the Fisher Exact Test; high dose, 77%, P<0.001) (females: 9%; 16%; 16%, p=0.211) and EC-7 (males: control, 17%; low dose, 40%, p=0.024; mid dose, 44%, p=0.009; high dose 69%, p<0.001) (females: 3%; 8%, p=0.322; 12%, p=0.135; 65%, p<0.001). The incidences of adrenal medullary pheochromocytomas were significantly increased in male, but not female mice exposed to PCP-T (males: 0%; 22%, p=0.003; 51%, p<0.001) and in both male and female mice exposed to EC-7 (males: 0%; 8% p=0.111; 44%, p<0.001; 92%, p<0.001) (females: 0%; 4%; 4%; 78%, p<0.001). In addition, the incidences of hemangiosarcomas were significantly increased in high-dose female mice that received both PCP-T (0%; 6%, p=0.198; 12%, p=0.036) and EC-7 (0%; 2%; 6%; 16%, p=0.010). The investigators concluded that under the conditions of these studies, there is clear evidence of carcinogenic activity for male B6C3F$_1$ mice fed diets containing technical-grade PCP and for male and female mice fed EC-7, and some evidence of carcinogenic activity for female mice fed diets containing technical-grade PCP.

39.3.1.2 Genotoxicity

The data concerning the mutagenicity of pentachlorophenol are conflicting, but the majority of test results are negative. Fahrig et al. (913) reported a significant increase in forward mutations and mitotic gene conversions in Saccharomyces cerevisiae following a 3.5-hour in vitro exposure to 400 mg/L PCP. No positive controls were run.

The same investigators reported weak mutagenic results in a spot test with mice; however, the results were inconclusive due to the lack of data on the controls and on the incidence of treatment-related maternal toxicity. Upon subsequent review, the data were determined not to be statistically significant (913).

Andersen et al. (915) reported that PCP did not induce revertants in eight histidine-requiring strains of Salmonella typhimurium; the tests did not employ liver microsomal activation. Simmon et al. (3653) also did not observe any increase in revertants in 5 strains of Salmonella tested with metabolic activation. PCP produced negative mutagenic responses in a host-mediated assay (916) and, in a Drosophila

sex-linked recessive lethal test, Vogel and Chandler (917) used the sodium salt of PCP and observed no increase in lethals compared with controls.

In studies with 2-amino-3-methylimidazo (4,5-f) quinoline (IQ), a known potent mutagen, Paterson and Chipman (3556) treated Salmonella typhimurium TA98 simultaneously with PCP and IQ and observed a significant reduction in the number of histidine revertants recovered compared with IQ treatment alone.

Jansson and Jansson (3335) treated Chinese hamster V79 cells with PCP for 24 hours and did not observe an increase in 6-thioguanine-resistant mutants at the HPRT locus. Similar results were obtained with the five other chlorophenols also tested. Galloway et al. (3235) tested PCP for the induction of sister chromatid exchanges and chromosome aberrations using Chinese hamster ovary cells and observed no increase in sister chromatid exchanges with metabolic activation (S9) and only a marginal increase without; chromosome aberrations were slightly increased with activation but stayed at control levels without activation.

In a human study, Bauchinger et al. (918) found a small but significant increase in the frequency of structural chromosome changes in the lymphocytes of 22 male workers employed in a PCP plant for up to 30 years. Chromosomal aberrations consisted of acentrics and dicentrics (i.e., lacking or having two centromeres, the portion of the chromosome to which the chromatids are joined). There was no significant increase in sister chromatid exchanges as compared with matched controls. An earlier study by Wyllie and coworkers (1200) found no significant difference in the incidence of chromosome breaks or gaps in 6 occupationally exposed workers when compared to 4 controls.

39.3.1.3 Teratogenicity, Embryotoxicity and Reproductive Effects

The embryonal and fetal effects of PCP in rats were assessed in a series of studies by Schwetz et al. (912). In one study, 5, 15, 30 or 50 mg/kg/day of purified PCP (PCP-P) (> 98%) or 5.8, 15, 34.7 or 50 mg/kg/day of commercial PCP (PCP-C) (88.4%) were administered by gavage to Sprague-Dawley rats on days 6 through 15 of gestation. Statistically significant, dose-related decreases in maternal weight gain were noted with both PCP samples at the top two treatment levels. In the offspring, PCP-P exerted a more pronounced effect than PCP-C. Fetal resorptions were statistically significant in dams given 15, 34.7 or 50 mg/kg/day of PCP-C or 30 or 50 mg/kg/day PCP-P. Resorption rates were 9, 27 and 58%, respectively, for PCP-C and 98 and 100%, respectively, for the PCP-P compared to 4.2% in controls. The no-effect levels for resorptions were 5.8 mg/kg PCP-C/day and 15 mg/kg PCP-P/day. The occurrence of subcutaneous edema, dilated ureters, and anomalies of the skull and vertebrae increased with increasing PCP dose (both grades) but were not significantly different from controls. Decreases in fetal body weight and crown rump length were seen at the upper dosage levels of either grade. Dosages of 15 mg/kg or less of either grade had no effects on fetal body measurements. In a second study, these investigators (912) showed that the developing rat embryo was more susceptible to a

given dose of PCP during the period of early organogenesis (days 8-11) than during the later period (days 12-15).

In a single generation reproduction study, Sprague-Dawley rats were fed 0, 3 or 30 mg/kg/day of purified PCP for 62 days prior to mating, throughout gestation and up to 21 days postpartum. The 30 mg/kg dose resulted in a significant decrease in the number of pups born alive and significantly decreased survival to days 7, 14 and 21 of lactation, but had no effect on fertility. A significantly increased number of litters showed skeletal anomalies at this dose, the average litter size was decreased and mean neonatal body weight was significantly less than controls. No adverse effects were noted at doses of 3 mg/kg/day (919). Similar results were observed when rats were exposed to purified PCP at dietary levels of 4, 13, or 43 mg/kg/day starting 181 days prior to mating and continuing through pregnancy (3834). Embryolethality was almost complete at the highest dose. At the lower doses, fetuses exhibited dose-related decreases in body weights, and at 13 mg/kg, an increase in skeletal variation was seen. No increase in teratogenicity was observed in either of these studies in the treated groups compared to the controls.

Daily oral administration of 1.25 to 20 mg/kg PCP to Syrian golden hamsters on days 5 to 10 of pregnancy resulted in fetal deaths and/or resorptions in three of six test groups (1201). No other data were provided.

39.3.1.4 Other Toxicologic Effects

39.3.1.4.1 Short-term Toxicity

Assessment of the toxicity data on PCP is complicated by the presence of varying quantities of tetrachlorophenols, dioxins, and furans in the technical-grade material. Some of the acute effects of PCP have been attributed to these contaminants, but typical adverse effects of the contaminants may not appear for several weeks (3961). The toxic effects of technical and pure PCP have been compared in several studies, but it is difficult, in some cases, to determine which effects are truly caused by PCP and which are due to the toxic contaminants (914).

The oral LD_{50} values in rodents range from 27-205 mg/kg (grade unspecified) (59, 3961). Fuel oil-type solvents reduce the lethal dose (i.e., increase toxicity), while aqueous solutions of the sodium salt are less toxic (910). The oral LD_{50} of purified PCP in the rat has been reported to be 150-200 mg/kg (924). Signs of acute intoxication result from the ability of PCP to uncouple oxidative phosphorylation; they include an increase in the basal metabolic rate and a subsequent rise in body temperature, respiratory rate and heart rate. Progressive neuromuscular weakness, with convulsions and cardiac failure are observed in fatal cases. Death is characterized by the rapid onset of rigor mortis (12, 924).

PCP readily penetrates the skin. A dermal LD_{50} of 96 mg/kg has been reported for the rat (3891). Local effects of skin contact depend upon the amount of

impurities in the sample. In a rabbit ear bioassay test using both pure PCP (PCP-P) and technical-grade PCP (PCP-T), a positive acnegenic response was noted with PCP-T which contained 1980 ppm octachlorodibenzo-p-dioxin and 19 ppm hexachlorodibenzo-p-dioxin (HCDD). PCP-P gave a negative response. Purified technical-grade PCP containing 1 ppm HCDD also gave a negative response (922).

In another dermal study, McGavack et al. applied varying amounts of aqueous PCP solutions of unspecified purity to the intact shaved skin of rabbits. Within 14 days, 1% PCP solutions produced redness, while 1.5% solutions caused microscopic evidence of skin irritation. A single application of a 10% PCP solution in doses ranging from 60 to 600 mg/kg produced swelling, inflammation, excoriation, desquamation and brown pigmentation of the skin (921).

The inhalation LC_{50} for PCP in rats is 335 mg/m^3 and for mice 225 mg/m^3 (3891). The most important acute effect of PCP inhalation occurs in the circulatory system with accompanying heart failure (3891).

PCP is a severe eye irritant (924). Rabbit eyes exposed to solid PCP showed conjunctival and iritic congestion (923).

39.3.1.4.2 Chronic Toxicity

Chronic exposure to technical-grade PCP produces a number of hepatic changes. Groups of 19 male and 5-15 female mice were fed diets containing either 0 or concentrations ranging from 20 to 12,500 ppm technical-grade pentachlorophenol (PCP-T), Dowicide EC-7, or pure pentachlorophenol (PCP-P) for 30 consecutive days (3927). All three compounds caused mortalities at 12,500 ppm, and EC-7 and PCP-P caused mortalities at 2,500 ppm. All treated groups, with the exception of those treated with 20 or 200 ppm EC-7, exhibited diffuse centrilobular cytomegaly, karyomegaly, nuclear atypia, degeneration, or necrosis of the liver.

In an 8-month study, Goldstein et al. (925) fed rats 20, 100 or 500 ppm technical PCP (PCP-T) or pure PCP (PCP-P) (equivalent to 1.2, 6 and 30 mg/kg, respectively). Feeding of 20 or 100 ppm PCP-P had no effect, but feeding of the PCP-T resulted in increased levels of liver enzymes and uroporphyrin. Body weight gain was reduced for both samples at 500 ppm PCP. Kociba et al. (926) also compared the toxicity of PCP-P versus PCP-T in a 90-day study with rats fed 3, 10 or 30 mg/kg/day. The investigators noted increased relative liver and kidney weights at all PCP-T treatment levels. With PCP-P, increased relative liver weights were noted at the top two treatment levels only and increased relative kidney weights were seen at the 30 mg/kg level. With PCP-T, focal hepatocellular degeneration and necrosis as well as elevated serum liver enzymes were observed in animals that received 30 mg/kg.

With a PCP sample that contained "low amounts" of non-phenolic impurities, Schwetz et al. (919) observed mild toxicity in weanling Sprague-Dawley rats fed 30 mg/kg/day in their diet for 2 years. This resulted in decreased body weight gain,

increased SGPT and increased urine specific gravity. The NOAEL was 3 mg/kg in females and 10 mg/kg in males.

Nonneoplastic adverse effects of the liver, spleen, and nose were observed in animals following oral administration of PCP for two years (3927). B6C3F$_1$ mice (50/sex/dose and 35/sex/control group) were given technical grade pentachlorophenol (PCP-T) in the diet at concentrations of 0, 100, or 200 ppm (17-18 or 35 mg/kg/day), or a commercial preparation, Dowicide EC-7, at concentrations of 0, 100, 200, or 600 ppm (17-18, 34-37, or 114-118 mg/kg/day) (3927). Survival was not affected by the doses of either chemical used in this study, but dose-related weight decreases were observed in high-dose mice given PCP-T and in mid- and high-dose mice given EC-7. The main liver lesions, induced by both compounds, included an increased incidence of clear cell foci, chronic active inflammation, pigmentation, necrosis, cytomegaly, proliferation of hematopoietic cells, and bile duct hyperplasia. In the spleens of the males and high-dose females treated with PCP-T the amounts of extramedullary hematopoiesis of the red pulp were increased. The high-dose mice that were treated with EC-7 had acute focal inflammation of the nasal mucosa and focal metaplasia of the olfactory epithelium.

The immune response in mice has been compromised by exposure to PCP. Holsapple et al. (3914) observed a dose-related suppression in the humoral antibody response to sheep red blood cells (SRBC) from female B6C3F$_1$ mice treated with technical-grade PCP (PCP-T). The mice were immunized with SRBC during 14 days of treatment with 0, 10, 30, or 100 mg/kg of PCP-T. The effect of the technical-grade compound was statistically significant ($p < 0.01$ or $p < 0.05$) at all doses. Purified PCP (PCP-P), administered over 14 days at the dose of 100 mg/kg, did not suppress the antibody response to SRBC when the mice were immunized during exposure; and neither PCP-T or PCP-P, administered to mice in vivo, affected the responses of spleen cell suspensions challenged with SRBC antigen in vitro. The investigators suggest that the lack of effect of PCP-T on cells subsequently challenged with antigen in vitro indicates that the immunosuppressive effect of PCP on animals challenged in vivo is not the result of a direct suppression of the functions of the immunocompetent cells. In contrast, both PCP-T and PCP-P suppressed in vitro antibody production in, and caused direct cytotoxicity to, spleen cells from untreated mice.

Kerkvliet et al. (927) found that PCP altered humoral immune functions in adult mice fed diets containing 50 or 500 ppm technical grade (86%) for 10-12 weeks. The animals also exhibited greatly enhanced tumor susceptibility to low-dose, sarcoma-tumor-cell challenge (67% and 82% tumor incidence in mice exposed to 50 and 500 ppm, respectively, compared to 35% for controls). No significant changes were noted in mice fed pure PCP (> 99%) for the same time period.

In another study, B6C3F$_1$ mice were treated for 26-27 weeks with technical-grade pentachlorophenol (PCP-T), commercial grade pentachlorophenol DP-2, Dowicide EC-7, or pure pentachlorophenol (PCP-P), at dietary concentrations ranging from 200

to 1800 ppm for 26-27 weeks (3927). The effect of these compounds on the humoral immune response was determined by measuring the hemagglutination (HA) titers and by quantitating the plaque-forming cell (PFC) response following immunization with sheep erythrocytes. The PFC response was markedly suppressed (approximately 9-fold) in mice exposed to PCP-T, and to a lesser degree (approximately 6-fold) in mice exposed to the high dose of DP-2, but was not affected by Dowicide EC-7 or PCP-P. The HA titers showed a similar trend, but were not as consistent, probably reflecting the lack of sensitivity of the assay.

39.3.2 Human and Epidemiologic Studies

39.3.2.1 Short-term Toxicologic Effects

PCP intoxication is characterized by weakness, fatigue, dizziness, headache, abdominal pain, congestion of ocular and nasal mucosae, profuse sweating and high fever (approximately equal to 106-108°F). PCP readily penetrates the skin and most cases of human exposure are through this route (909). Bevenue et al. (928) reported reddening and painful sensations in the hands of a male 10 minutes after immersion of his hands in a 0.4% PCP solution. The pain persisted for 2 hours. Urinary PCP levels returned to background levels within one month. Local skin irritation and chloracne have also been associated with dermal contact to technical PCP but dioxin contaminants are believed to be the causative agents in these cases (909).

Dust and mist concentrations greater than 1 mg/m^3 cause sneezing coughing and painful irritation of the eyes, nose and throat and 0.3 mg/m^3 may cause some nose irritation. Up to 2.4 mg/m^3 can be tolerated by persons acclimated to PCP (38).

Sangster et al. (929) reported symptoms of a generalized itching dermatosis, drowsiness, nausea, loss of appetite, swelling of the eyelids and dryness and scaling of the face and hands in 15 members of 3 families living in houses where large volumes of PCP solutions (5 to 5.5%) had been applied to the timbers and/or furniture. Plasma PCP concentrations ranged from 25 to 660 μg/L; the mean plasma PCP concentration in 99 military draftees used as a control population was 128 μg/L.

Throat irritation, facial flushing and hand and leg weakness were noted in 4 families after drinking and bathing in water from a well containing 12.5 mg/L PCP. Recovery occurred within 2-3 days (928). In a similar case, a 4-year-old child was hospitalized with fever, intermittent delirium, acidosis, aminoaciduria and ketonuria after bathing daily for 13 days with water from a PCP-contaminated holding tank (930).

Twenty newborn infants, exposed to PCP used in laundering diapers and bed linen, subsequently exhibited tachycardia, respiratory distress, and liver changes (3935). Two of the twenty infants died and autopsy revealed degeneration of the kidney and effects on the liver.

Numerous industry-related PCP fatalities have been reported. Among the changes reported at autopsy were edematous brain and lungs, tubular degeneration of the kidneys, congestion of the liver with centrilobular degeneration, and heart dilation (931). Splenomegaly and renal congestion have also been observed (3961). In fatal cases, the body temperature may be extremely high and death may occur as early as 3 hours after the onset of symptoms (46). Survivors of PCP intoxication are affected by impairments in autonomic function, circulation, visual damage, and acute scotoma (3891).

A recent report of a fatal case involved a 33-year-old chemical plant worker who had been breaking up blocks of PCP. For 2 weeks prior to hospital admission, he experienced lethargy, breathing difficulties, profound thirst and sweating. On admittance to the hospital, the worker was comatose, his respiratory rate was 56/minute and his rectal temperature was 105°F. The patient succumbed 1 hour after admission despite treatment aimed at control of body temperature. Postmortem examination revealed an extreme degree of rigor in the thigh and leg muscles, edema of the brain and lungs and congestion of the liver (932). Subsequent analysis of the victim's tissues revealed markedly elevated levels of polychlorinated dibenzodioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs), common contaminants of technical PCP (3939). These compounds are present in the adipose tissues of all individuals from industrialized countries. In the adipose tissue of the victim, the levels of hepta-PCDDs/PCDFs and octa-PCDDs/PCDFs were over 100 times greater than background levels. Liver tissue also contained elevated levels of the contaminants. Smaller concentrations of other isomers that do occur in significant amounts in PCP, but are not normally present in human tissues, were also found in the tissues. Although the significance of the PCDDs and PCDFs in the toxicity of PCP was not clear, the investigators indicated that these compounds must have affected the health of the victim in an adverse way and may have aggravated or modified the effects of the high levels of PCP.

PCP has also been reported to cause conjunctival irritation, corneal opacity, corneal numbness and slight mydriasis (3891).

39.3.2.2 Chronic Toxicologic Effects

Symptoms of chronic toxicity are similar to those seen in acute intoxications. These include muscle weakness, headache, anorexia, abdominal pain and weight loss in addition to skin, eye and respiratory tract irritation (910). Another chronic health effect associated with commercial PCP exposure is chloracne, a type of acneform dermatitis commonly associated with exposure to dioxins. Baader and Bauer (933) reported chloracne in 10 workers engaged in PCP production for 5-10 months. Seven of these workers also developed severe bronchitis. More than one year after cessation of exposure, all but one worker still showed signs of extensive dermatitis and 4 still complained of bronchitis. One fatal case of aplastic anemia has been linked to dermal exposure to PCP for one year (934).

Long-term exposure to PCP may also affect the liver, kidneys and nervous system but interpretation of the data are complicated by the presence of PCP impurities as well as solvents. Among the effects reported with occupational exposure were liver enzymes which were elevated but still within normal limits (936) and reversible decreases in glomerular filtration rate and renal tubular function (935). One study suggests that PCP may alter human immune response as evidenced by a higher incidence of low-grade infection and inflammations in PCP-exposed workers (938). Another study demonstrated significant decreases in IgA and IgG immunoglobulins among workers exposed to PCP (3928). Slight decreases in nerve conduction velocity were observed in a cross-sectional study (in 1980) of chemical workers exposed to PCP and PCP-containing substances (937). However, these effects were not observed in a longitudinal study (1980-1984) of the same population exposed for an average of 16 years to concentrations of 0.3 to 180 $\mu g/m^3$ (3946). The investigators concluded that occupational exposure to PCP over several years at the concentrations observed probably does not adversely affect the peripheral nervous system.

Recently there have been several reports suggesting a possible association between PCP use and production and development of leukemia, Hodgkin's disease and soft tissue sarcomas. PCP exposure could not be distinguished from dioxin exposure in any of these studies and in some cases, exposure to other chemicals also occurred. IARC (25) considers this evidence to be inadequate for assessment of human carcinogenicity of PCP.

39.3.3 Levels of Concern

The USEPA (3770) has established a water quality criterion for PCP of 1.01 mg/L for the protection of public health. The criterion is based on the oral no-observed adverse effect level of 3 mg/kg for the rat (919) and an uncertainty factor of 100. An Oral Reference Dose of 30 $\mu g/kg/day$ has been proposed by the USEPA L37445.

The USEPA (992) has developed the following Health Advisories for noncarcinogenic risks for PCP concentrations in drinking water: 1 day (10 kg child), 1.0 mg/L; 10 days (10 kg child), 0.3 mg/L; longer-term (10 kg child), 0.3 mg/L; longer-term (70 kg adult), 1.0 mg/L; and lifetime (70 kg adult), 0.200 mg/L (3954).

The World Health Organization (666) has proposed a health-based guideline of 10 $\mu g/L$ PCP for drinking water; daily per capita consumption of two liters of drinking water was assumed.

IARC (803) lists PCP in category 3 (insufficient evidence) in its weight-of-evidence ranking for potential carcinogens. The NTP has not assigned a classification as yet to PCP; studies are in progress.

OSHA (3539) currently permits and the ACGIH (3005) recommends that exposure to PCP be limited to 0.5 mg/m³ averaged over an 8-hour work shift. These exposure limits were selected to prevent systemic toxicity.

39.3.4 Hazard Assessment

PCP may be absorbed through the skin, by inhalation or by ingestion. Assessment of the toxicity of PCP is complicated by the presence of varying amounts of toxic contaminants; grades of purity range from 86% to >99%.

Acute exposure hazards for PCP result from its ability to uncouple oxidative phosphorylation and inhibit mitochondrial ATPase, causing a markedly increased metabolic rate and elevated body temperature. Risk of serious intoxication with PCP is increased in hot weather. Human fatalities have been documented (931, 932). Long-term exposure to PCP produces hepatic and renal changes in laboratory animals (925, 926) and humans (931, 932, 935, 936) and may compromise immune response (927, 938, 3927). Absorption of PCP by any route may result in chloracne in humans (933).

Technical-grade and a commercial grade of PCP have been evaluated for carcinogenicity in rats and three strains of mice. In one study rats ingested up to 30 mg/kg/day of technical PCP for 2 years, while in another, mice ingested up to 46.4 mg/kg/day. No increased incidences of tumors were seen (911, 919). In a recently completed NTP bioassay, in which mice were fed technical PCP doses of up to 35 mg/kg/day and commercial PCP doses of up to 118 mg/kg/day for two years, there was clear evidence for carcinogenicity of technical (males and females) and commercial (males only) grades of PCP (3827). There are limited data to suggest possible mutagenic activity for PCP but the majority of mutagenic test results are negative.

Embryotoxic and fetotoxic effects such as resorptions, subcutaneous edema, dilated ureters and anomalies of the skull and ribs were observed in rats exposed to PCP during gestation (912, 919). Purified PCP appears to be somewhat more toxic than technical-grade PCP with respect to embryonal and fetal effects. A no-observed adverse effect level of 3 mg/kg/day of purified PCP was recorded for rats (919).

39.4 SAMPLING AND ANALYSIS CONSIDERATIONS

Determination of pentachlorophenol concentrations in soil and water requires collection of a representative field sample and laboratory analysis. Soil and water samples are collected in glass containers; extraction of samples should be completed within 7 days of sampling and analysis completed within 30-40 days. In addition to the targeted samples, quality control samples such as field blanks, duplicates, and fortified sample matrices may be specified in the recommended methods.

EPA-approved procedures for the analysis of pentachlorophenol, one of the EPA priority pollutants, in aqueous samples include EPA Methods 604, 625 and 1625 (65), 8040 and 8250 (63). Prior to analysis, samples are extracted with methylene chloride as a solvent using a separatory funnel or a continuous liquid-liquid extractor. Methods 604 and 8040 also provide for a perfluorobenzyl bromide (PFB) derivatization of the sample extract with additional clean-up procedures if interferences are present in the sample matrix. An aliquot of the concentrated sample extract with or without derivatization is injected onto a gas chromatographic (GC) column using a solvent flush technique. The GC column is programmed to separate the semi-volatile organics; pentachlorophenol is then detected with a flame ionization detector (Methods 604 and 8040 without derivatization), as its PFB derivative with an electron capture detector (Methods 604 and 8040 with derivatization) or with a mass spectrometer (Methods 625, 1625, and 8250).

The EPA procedures recommended for pentachlorophenol analysis in soil and waste samples, Methods 8040 and 8250 (63), differ from the aqueous procedures primarily in the preparation of the sample extract. Solid samples are extracted using either soxhlet extraction or sonication methods. Neat and diluted organic liquids may be analyzed by direct injection.

Other methods that have been described for the determination of pentachlorophenol include differential pulse cathodic-stripping voltammetry (3065) and isotope-dilution GC-MS (3404). The compound has also been analyzed by high performance liquid chromatography using reversed-phase columns and electrochemical detection (3440) or UV absorbance, monitoring at 254 and/or 230 nm (3437). This latter method is only appropriate for relatively high concentrations in the 20 to 500 ppm range. Electrochemical detection on the other hand provide very sensitive detection, to 1 ppb depending on the matrix and background.

Typical pentachlorophenol detection limits that can be obtained in wastewaters and non-aqueous samples (wastes, soils, etc.) are shown below. The actual detection limit achieved in a given analysis will vary with instrument sensitivity and matrix effects.

Aqueous Detection Limit
- 7.4 µg/L (Method 604 without derivatization)
- 0.59 µg/L (Method 604 with derivatization)
- 3.6 µg/L (Method 625
- 74 µg/L (Method 8040 without derivatization)
- 5.9 µg/L (Method 8040 with derivatization)
- 36 µg/L (Method 8250)
- 50 µg/L (Method 1625)

Non-Aqueous Detection Limit
- 1.8 µg/g (Method 8040 without derivatization)
- 0.4 µg/g (Method 8040 with derivatization)
- 2.4 µg/g (Method 8250)

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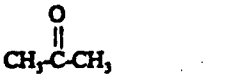
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COMMON SYNONYMS:	CAS REG.NO.: 67-64-1 FORMULA: C_3H_6O NIOSH NO: AL3150000 STRUCTURE: 	AIR W/V CONVERSION FACTOR at 25°C (12) 2.37 mg/m³ ≈ 1 ppm; 0.422 ppm ≈ 1 mg/m³ MOLECULAR WEIGHT: 58.09
2-Propanone Acetone Dimethyl ketone Methyl acetal Methyl ketone Pyroacetic acid Pyroacetic ether		

REACTIVITY	Reactions of ketones such as acetone with cyanides, mercaptans or other organic sulfides typically produce heat, while those with alkali or alkaline earth elemental metals, nitrides or strong reducing agents evolve heat and flammable gases. Reactions with oxidizing mineral acids or other strong oxidizing agents may generate heat, fires, and/or explosions. Those with azo or diazo compounds or hydrazines may generate heat and usually innocuous gases. Reactions with organic peroxides or hydroperoxides typically result in explosions, while those with chlorinated melamines may result in rapid reaction, fumes, fire, and explosion. Explosive reactions have also been reported with chloroform and a base (not given), and with nitrosyl chloride and a platinum catalyst in closed containers (505, 511).

PHYSICO-CHEMICAL DATA	• Physical State: Liquid, volatile (at 20°C)	(45)
	• Color: Colorless	(45)
	• Odor: Sweet, pungent	(45)
	• Odor Threshold: 20.000 ppm	(13)
	• Density: 0.7910 g/mL (at 20°C)	(21)
	• Freeze/Melt Point: -95.30°C	(23)
	• Boiling Point: 56.20°C	(13)
	• Flash Point: -20.00 to -17.00°C (closed cup) -15.6 to -9.4°C, (open cup)	(23,51,60) (507)
	• Flammable Limits: 2.15 or 2.6 to 12.80% by volume	(51,60,506) (507)

PHYSICO-CHEMICAL DATA (Cont.)	• Autoignition Temp.: 465.0, 538.0 or 560.0°C	(23,51,506) (514)
	• Vapor Pressure: 1.86E+02 mm Hg (at 20°C)	(21)
	• Satd. Conc. in Air: 5.9000E+05 mg/m^3 (at 20°C)	(1219)
	• Solubility in Water: Infinite	(21)
	• Viscosity: 0.330 cp (at 20°C)	(21)
	• Surface Tension: 2.3700E+01 dyne/cm (at 20°C)	(21)
	• Log (Octanol-Water Partition Coeff.): -0.24	(29)
	• Soil Adsorp. Coeff.: 2.80E-01	(65)
	• Henry's Law Const.: 3.97E-05 $atm \cdot m^3/mol$ (at 25°C)	(966)
	• Bioconc. Factor: 3.00E-02 (estim)	(659)

PERSISTENCE IN THE SOIL-WATER SYSTEM	Acetone is expected to migrate freely through the soil/ground-water system. Volatilization may occur in near surface soils; however, vapor phase concentrations in soil are expected to be very low whenever water is present. Biodegradation of acetone has been demonstrated and persistence in environments with active microbial populations is not expected.

PATHWAYS OF EXPOSURE	The primary pathway of concern from a soil/ground-water system is the migration of acetone to groundwater drinking water supplies. Inhalation may be important in some situations. Bioaccumulation of acetone is not likely to be an important exposure pathway.

HEALTH HAZARD DATA	Signs and Symptoms of Short-term Human Exposure: (2, 46) Dryness and irritation of eyes, nose and throat are usual signs of acute exposure to acetone vapor. Exposure to high concentrations of acetone can produce dizziness, nausea, narcosis and in extreme cases, coma. Acute Toxicity Studies: (3504) INHALATION: LC_{50} 110,000 mg/cm^3 · 62 minutes — Mouse LC_{50} 50,100 mg/m^3 · 8 hr — Rat TC_{LO} 440 mg/m^3 · 6 min — Man ORAL: LD_{50} 9750 mg/kg — Rat LD_{50} 5800 mg/kg — Rat LD_{50} 3000 mg/kg — Mouse LD_{50} 5340 mg/kg — Rabbit TD_{LO} 2857 mg/kg — Man SKIN: LD_{50} 20,000 mg/kg — Rabbit Long-Term Effects: Respiratory tract irritation, dermatitis Pregnancy/Neonate Data: Not teratogenic in chickens Genotoxicity Data: Primarily negative Carcinogenicity Classification: IARC - No data NTP - In review EPA - No data

HANDLING PRECAUTIONS (54)	Handle chemical only with adequate ventilation • Vapor concentrations of 750-5000 ppm: respirator with organic vapor canister • Vapor concentrations of 5000-20,000 ppm: NIOSH approved respirator with organic vapor canister; any supplied air respirator or self-contained breathing aparatus with full facepiece • Butyl, natural rubber, neoprene, nitrile, PE, PVA, or PVC gloves, apron and boots to prevent repeated or prolonged skin contact with the liquid • Chemical goggles if there is probability of eye contact.

ENVIRONMENTAL AND OCCUPATIONAL STANDARDS AND CRITERIA

AIR EXPOSURE LIMITS:

Standards
- OSHA TWA (8-hr): 750 ppm; STEL (15-min): 1000 ppm
- AFOSH PEL (8-hr TWA): 750 ppm; STEL (15-min): 1000 ppm

Criteria
- NIOSH IDLH (30-min): 20,000 ppm
- NIOSH REL (10-hr TWA): 250 ppm
- ACGIH TLV® (8-hr TWA): 750 ppm
- ACGIH STEL (15-min): 1000 ppm

WATER EXPOSURE LIMITS:

Drinking Water Standards
None established

EPA Health Advisories and Cancer Risk Levels
None established

WHO Drinking Water Guideline
No information available.

EPA Ambient Water Quality Criteria
- Human Health (355)
  - No criterion established; acetone is not a priority pollutant.
- Aquatic Life (355)
  - No criterion established; acetone is not a priority pollutant.

REFERENCE DOSES: (3744)
ORAL: 1.000E-01 mg/kg/day

REGULATORY STATUS (as of 01-MAR-89)

Promulgated Regulations

- Federal Programs

Safe Drinking Water Act (SDWA)
In states with an approved Underground Injection Control program, a permit is required for the injection of acetone-containing wastes designated as hazardous under RCRA (295).

Resource Conservation and Recovery Act (RCRA)
Acetone is identified as an ignitable hazardous waste (U002) (3784). Non-specific sources of acetone-containing waste that contain at least 10% acetone are solvent use (or recovery) activities (325). Solvent washes and sludges from the ink formulation industry contain acetone and are listed as specific sources of hazardous waste (3774 3765). Effective November 8, 1988, spent solvent hazardous wastes containing acetone are prohibited from land disposal. Certain variances exist until May, 1990 for wastewaters, nonwastewaters, and contaminanted soils for which Best Demonstrated Available Technology (BDAT) treatment standards have not been promulgated by EPA (3786) Acetone is included on EPA's ground-water monitoring list. EPA requires that all hazardous waste treatment, storage, and disposal facilities monitor their ground-water for chemicals on this list when suspected contamination is first detected and annually thereafter (3775).

Comprehensive Environmental Response Compensation and Liability Act (CERCLA)
Acetone is designated a hazardous substance under CERCLA. It has a reportable quantity (RQ) limit of 2270 kg. Reportable quantities have also been issued for RCRA hazardous waste streams containing acetone but these depend upon the concentrations of the chemicals in the waste stream (3766). Under SARA Title III Section 313, manufacturers, processors, importers, and users of acetone must report annually to EPA and state officials their releases of this chemical to the environment (3787).

Federal Insecticide, Fungicide and Rodenticide Act (FIFRA)
Acetone is exempt from a tolerance requirement when used as a solvent in pesticide formulations applied to growing crops or to raw agricultural commodities after harvest (315).

Marine Protection Research and Sanctuaries Act (MPRSA)
Ocean dumping of organohalogen compounds as well as the dumping of known or suspected carcinogens, mutagens or teratogens is prohibited except when they are present as trace contaminants. Permit applicants are exempt from these regulations if they can demonstrate that such chemical constituents are non-toxic and non-bioaccumulative in the marine environment or are rapidly rendered harmless by physical, chemical or biological processes in the sea (309).

Occupational Safety and Health Act (OSHA)
Employee exposure to acetone shall not exceed an 8-hour time-weighted average (TWA) of 750 ppm or a 15-minute short-term exposure limit (STEL) of 1000 ppm (3539).

Hazardous Materials Transportation Act (HMTA)
The Department of Transportation has designated acetone as a hazardous material with a reportable quantity of 2270 kg, subject to requirements for packaging, labeling and transportation (3180).

Food, Drug and Cosmetic Act (FDCA)
Acetone is approved for use as an indirect food additive as a component of adhesives (3209). A tolerance of 30 ppm is established for acetone in spice oleo-resins when present as a residue from extraction of spice (361).

- State Water Programs

ALL STATES
All states have adopted EPA Ambient Water Quality Criteria and NPDWRs (see Water Exposure Limits section) as their promulgated state regulations, either by narrative reference or by relisting the specific numeric criteria. These states have promulgated additional or more stringent criteria:

NEW YORK
New York has set an MCL of 50 μg/L for acetone in drinking water (3501).

OKLAHOMA
Oklahoma has a water quality criterion of 2.7 μg/L for acetone in ground-water (3534).

SOUTH DAKOTA
South Dakota requires acetone to be nondetectable, using designated test methods, in ground-water (3671).

Proposed Regulations

- Federal Programs

  No proposed regulations are pending.

- State Water Programs

  MOST STATES

  Most states are in the process of revising their water programs and proposing changes in their regulations which will follow EPA's changes when they become final. Contact with the state officer is advised. Changes are projected for 1989-90 (3683).

  MINNESOTA

  Minnesota has proposed a Recommended Allowable Limit (RAL) of 700 µg/L for drinking water (3451). Minnesota has also proposed a Sensitive Acute Limit (SAL) of 3,800,000 µg/L for designated surface waters, and chronic criteria of 686 µg/L for designated surface waters and 700 µg/L for designated ground-waters. These criteria are for the protection of human health (3452).

EEC Directives

Directive on Marketing and Use of Dangerous Substances (541)
Acetone may not be used in ornamental objects intended to produce light or color effects by means of different phases.

Directive on the Classification, Packaging and Labeling of Dangerous Substances (787)
Acetone is classified as a flammable substance and is subject to packaging and labeling regulations.

Directive relating to the Classification, Packaging and Labeling of Dangerous Preparations (Solvents) (544)
Acetone is listed as a Class II/ a harmful substances and is subject to packaging and labeling regulations.

EEC Directive-Proposed
Resolution on a Revised List of Second-Category Pollutants (545)
Acetone is one of the second-category pollutants to be studied by the Commission in the programme of action of the European Communities on Environment in order to reduce pollution and nuisances in the air and water. Risk to human health and the environment, limits of pollutant levels in the environment, and determination of quality standards to be applied will be assessed.

40.1 MAJOR USES

Acetone is used primarily as a solvent and chemical intermediate. Uses include the production of lubricating oils and as an intermediate in the manufacturing of chloroform and of various pharmaceuticals and pesticides. Acetone can also be found in paints, varnishes and lacquers and is used as a solvent for cements in the leather and rubber industry (54, 2, 59).

40.2 ENVIRONMENTAL FATE AND EXPOSURE PATHWAYS

40.2.1 Transport in Soil/Ground-water Systems

40.2.1.1 Overview

Acetone is expected to be mobile in the soil/ground-water system when present at relatively low concentrations or as a separate organic phase (resulting from a spill of significant quantities of the chemical). In general, transport pathways can be assessed by using an equilibrium partitioning model, as shown in Table 40-1. These calculations predict the partitioning of low soil concentrations of acetone among soil particles, soil water and soil air. Portions of acetone associated with the water and air phases of the soil have higher mobility than the adsorbed portion.

Estimates for the unsaturated topsoil model indicate that only 5.1% of the acetone is expected to be sorbed onto soil particles. Approximately 94% is expected to partition to the soil-water phase, and is thus available to migrate by bulk transport (e.g., the downward movement of infiltrating water), dispersion and diffusion. For the small portion of acetone in the gaseous phase of the soil (0.5%), diffusion through the soil-air pores up to the ground surface, and subsequent removal by wind, may be a significant loss pathway.

In saturated, deep soils (containing no soil air and negligible soil organic carbon), almost all of the acetone (99.9%) is predicted to be present in the soil-water phase (Table 40-1) and available for transport with flowing ground-water. Sorption onto deep soils (0.1%) is not expected to be significant. Overall, ground water underlying acetone-contaminated soils with low organic content is expected to be vulnerable to contamination.

40.2.1.2 Sorption on Soils

The mobility of acetone in the soil/ground-water system (and its eventual migration into aquifers) is governed by the extent of its sorption on soil particles. In general, sorption on soils is expected to:

TABLE 40-1
EQUILIBRIUM PARTITIONING CALCULATIONS FOR ACETONE IN MODEL ENVIRONMENTS[a]

Soil Environment	Estimated Percent of Total Mass of Chemical in Each Compartment		
	Soil	Soil-Water	Soil-Air
Unsaturated topsoil at 25°C[c]	5.1	94.4	0.5
Saturated deep soil[d]	0.1	99.9	-

a) Calculations based on Mackay's equilibrium partitioning model (34, 35, 36); see Introduction in Volume 1 for description of model and environmental conditions chosen to represent an unsaturated topsoil and saturated deep soil. Calculated percentages should be considered as rough estimates and used only for general guidance.
b) Utilized estimated soil sorption coefficient: K_{oc} = 0.28 (611).
c) Henry's law constant taken as 3.97E-05 atm · m³/mol at 25°C (966).
d) Used sorption coefficient K_p = 0.001 x K_{oc}.

- increase with increasing soil organic matter content;
- increase slightly with decreasing temperature;
- increase moderately with increasing salinity of the soil water; and
- decrease moderately with increasing dissolved organic matter in the soil water.

Acetone is infinitely soluble in water and, as evidenced by its negative log K_{ow} and low K_{oc}, adsorption to soil/sediments is not expected to contribute significantly to its environmental fate. Acetone has been detected in various types of water including drinking water; it has also been identified in leachates from landfills (1119).

Some sorption, however, has been reported. Rathbun et al. (1119) report studies indicating that acetone vapor was slightly sorbed to montmorillonite, but only if the clay was previously hydrated with water. Adsorption of acetone on activated carbon was also reported.

Green et al. (1122) provided data on the permeability of acetone in Ranger Shale, Kosse Kaoline, and Fire Clay. All three clay-soils are classified as virtually impervious to solvents and were observed to be more permeable to water than to solvents. The characteristics of the clay-soils and the reported permeability are

presented in Table 40-2. Of the compounds tested, acetone was the most mobile organic solvent in all matrices except Ranger Shale. (It was postulated that microbial decomposition of acetone in the biologically active Ranger Shale resulted in CO_2 production and clogging of pores.) Data from this study also indicate that the solvent that caused the greatest swelling (H_2O) had the highest coefficient of permeability; swelling reported for acetone was also relatively high.

In summary, acetone is expected to migrate freely through the soil/ground-water system with little or no retardation. Permeability to acetone has also been shown for materials known to be relatively impervious to organic solvents (e.g., clays).

40.2.1.3 Volatilization from Soils

In spite of the fact that acetone is a volatile compound, the potential for volatilization is reduced due to its high aqueous solubility. Transport of vapors through the air-filled pores of unsaturated soils may occur in near-surface soils. However, modeling results suggest that a very small fraction of the acetone loading will be present in the soil-air phase.

In general, important soil and environmental properties influencing the rate of volatilization include soil porosity, temperature, convection currents and barometric pressure changes; important physicochemical properties include the Henry's law constant, the vapor-soil sorption coefficient and, to the lesser extent, the vapor phase diffusion coefficient (31).

The Henry's law constant (H), which provides an indication of a chemical's tendency to volatilize from solution, is expected to increase significantly with increasing temperature. Moderate increases in H have also been observed with increasing salinity and the presence of other organic compounds (18). These results suggest that the presence of other materials may significantly affect the volatilization of acetone, particularly from surface soils. No information was available for the two other physico-chemical properties influencing volatilization, i.e., the vapor-soil sorption coefficient and the vapor phase diffusion coefficient.

Volatilization coefficients (K_v) for acetone in water have been reported (1119, 1121) to range from 0.6 $days^{-1}$ to 2.3 $days^{-1}$, corresponding to half-lives of 1.3 days to 0.34 days, for very low mixing conditions to very high mixing conditions, respectively. Experimental conditions used correspond to low air mixing, variable stirring rate of 0 - 2020 rpm and water depths of 200-267 mm. It is expected that these coefficients would increase for higher mixing conditions or increased air velocity in environmental aquatic systems.

TABLE 40-2
PERMEABILITY OF ACETONE IN THREE CLAY-SITES

	Ranger Shale	Kosse Kaoline	Fire Clay
Packed density (g/cc)	1.73	1.36	1.81
% Organic carbon	0.28	0.12	0.03
% Swell (H_2O)	11.7	11.7	8.2
% Swell (acetone)	4	8.7	3.6
Permeability (x 10^{-9} cm/sec) for H_2O	38	220	13.5
Permeability (x 10^{-9} cm/sec) for acetone	2.5	65	7

Source: Green et al. (1122)

The significance of acetone volatilization in the environment is not well known; data on volatilization from soils, in particular, are not available. Since acetone is not strongly adsorbed to soil, some volatilization at the surface may occur; however, the ability of acetone to be transported with soil water is significant. Furthermore, any acetone lost due to volatilization will be rapidly washed out of the atmosphere, due to its high water solubility, and returned to the soil/water system.

40.2.2 Transformation Processes in Soil/Ground-water Systems

The portion of acetone that has been released from the soil into the air will either return to the soil via atmospheric washout or eventually undergo photochemical oxidation; a photodissociation lifetime of 14.8 days has been reported for acetone in air under tropospheric conditions (1120).

No information on the hydrolysis of acetone was available; under normal environmental conditions, hydrolysis is not expected to occur at a rate competitive with volatilization or biodegradation. Rathbun et al. (1119) reported no significant photodegradation of acetone in water.

Acetone is expected to be highly susceptible to microbial biodegradation. It is rapidly oxidized by most sewage microorganisms (1130) and has been classified as having low persistence (1123-1125). Several authors (1132, 1133) have reported the biodegradation of acetone by microbes grown on acetone or propane, or by soil bacteria grown on C1-C8 aliphatic hydrocarbons. No acetone degradation with four yeast cultures was reported (1131).

Degradation of acetone, determined by BOD_t tests with acclimated sewage seed or microbes from polluted waters, ranged from 37% to 84%; degradation after 20 days was observed to be 76% to 84% (881, 880, 1127, 1134). Experimental biodegradation results (1119) with initial concentrations of 16 - 158 mg/L acetone showed the importance of acclimation of a bacterial culture to acetone. Without acclimation, the lag time before degradation averaged about 13 hours; with pretreatment, the lag time was reduced to 1.8 hours. The degradation coefficient (K_t) showed considerable scatter and ranged from 0.43 to 7.9 $days^{-1}$; there was no clear correlation of degradation rate with acclimation. Chou et al. (1126) reported 55% utilization of acetone in an anaerobic reactor.

Two studies (1128, 1129) reported some toxicity to activated sludge and domestic sewage seed at acetone concentrations of 500 mg/L.

In actual soil/ground-water systems, the concentration of microorganisms capable of biodegrading acetone may be low, and is expected to drop off sharply with increasing depth; prediction of biodegradation rates in the environment is not possible. However, persistence of acetone in environments with sufficient active microbial populations is not expected.

40.2.3 Primary Routes of Exposure from Soil/Ground-water Systems

The above discussion of fate pathways suggests that acetone has a moderate volatility, is very weakly adsorbed to soil, and has no significant potential for bioaccumulation. This compound may volatilize from the soil surface, but that portion not removed by volatilization is likely to be mobile in ground-water. These fate characteristics suggest several potential exposure pathways.

Volatilization of acetone from a disposal site could result in inhalation exposure to workers or residents in the area. In addition, the potential for ground-water contamination is high, particularly in sandy soils. Acetone has been detected in ground-water associated with hazardous waste sites. Mitre (83) reported that acetone has been found at 8 of the 546 National Priority List (NPL) sites. It was detected at 3 sites in ground-water, 3 in surface water and 3 in air. However, analysis for acetone may not be commonly done at NPL sites as it is not a priority pollutant and is not generally considered a public health concern. These data, as well as the properties of acetone, suggest that drinking water exposure from ground-water contamination is likely to be its primary route of exposure from soil/ground-water systems.

The movement of acetone in ground-water may result in discharge to surface water. As a result, ingestion exposures may occur resulting from the use of surface waters as drinking water supplies; dermal exposures may result from the recreational use of contaminated surface waters. Such exposures are likely to be lower than those obtained from drinking contaminated ground-water due to biodegradation and/or

volatilization of acetone in surface water. Any pathways related to the uptake of acetone by aquatic organisms or domestic animals from surface waters are likely to be less significant than other sources of exposure due to the low BCF for acetone.

40.2.4 Other Sources of Human Exposure

Acetone is a widely used industrial solvent. As such, there are a number of potential sources of human exposure. However, data to support these exposures are lacking. For example, acetone is not commonly measured in drinking water.

The production and use of acetone has led to its presence in the atmosphere. Brodzinsky and Singh (84) summarized air monitoring data for a number of pollutants. For acetone, they reported 22 data points for source-dominated areas. The median concentration reported was 0.83 $\mu g/m^3$. Acetone was also detected in the indoor air of an energy-efficient office building at approximate levels of 1-75 ppb (906).

Dermal exposure is expected to be common due to the prevalence of acetone as a solvent in various products. For example, two surveys were conducted in Japan on the solvent content of a variety of products. They found acetone in 4% of the paints, 4% of the inks, 12% of the adhesives, 9% of the thinners, and 8% of the degreasers that were sampled. While most of these products were used in occupational settings, some may be used by consumers (1140, 1141).

40.3 HUMAN HEALTH CONSIDERATIONS

40.3.1 Animal Studies

40.3.1.1 Carcinogenicity

The data available regarding the carcinogenicity of acetone are limited to a skin-painting study in mice of inadequate time duration. Van Duuren et al. (1043) applied 0.1 ml of acetone to the skin of female ICR/Ha Swiss mice three times a week for one year. No evidence of tumors were reported up to 208 days later.

40.3.1.2 Genotoxicity

Acetone has been used routinely as a solvent in many experiments testing chemicals for genotoxicity. It has seldom shown any positive effects.

Acetone was negative in a reverse mutation assay with the 5 standard strains of Salmonella typhimurium, both with and without metabolic activation (1017, 1054). Woodruff et al. (3846), in a validation study for the National Toxicology Program, found acetone to be negative in inducing sex-linked recessive lethals when adult males were either fed or injected with acetone.

Acetone did significantly inhibit metabolic cooperation in Chinese hamster V79 cells. This inhibition of metabolic cooperation is indicative of an inhibition of intercellular communication (1013). Ishidate et al. (3331) reported positive results in a chromosomal aberration assay in which Chinese hamster lung cells were treated in vitro with 10 mg/mL for 24 hrs; this result may be artifactual, for the number of aberrations at 20 and 30 mg/mL is at control levels. Zimmermann et al. (1011) reported that acetone induces aneuploidy in the D61.M strain of Saccharomyces cervisiae, but not point mutations or recombination. The incidence of aneuploidy in this organism can be increased when normal growth is interrupted by storing the cells with acetone in an ice bath.

Lasne et al. (3390) added 5 μL/mL acetone to Chinese hamster V79 cells to determine the effect of chemicals in inducing sister chromatid exchanges and micronuclei, and did not observe any increase over the culture medium controls. Von der Hude et al. (3819) did not observe an increase in sister chromatid exchanges in V79 cells tested with and without metabolic activation at concentrations up to 100 mM of acetone.

In an in vivo test, Basler (3055) injected male and female hamsters intraperiteonally with 865 mg/kg acetone and sacrificed them 12, 24, 48 or 72 hrs after treatment; no increase in micronucleated cells in their femoral bone marrow was observed.

40.3.1.3 Teratogenicity, Embryotoxicity and Reproductive Effects

McLaughlin et al. (1042) injected 39 or 78 mg acetone/kg into the yolk sac of fresh fertile chick eggs before incubation. The eggs were then incubated and hatched. Reduced hatchability was shown at both the 39 mg level (80% hatchability) and the 78 mg level (50% hatchability). The percent hatchability for control eggs (i.e., injected with needle only) was not reported. No evidence of teratogenicity was found at either treatment level.

Kitchin and Ebron (3363) studied the in vitro embrytoxicity and dysmorphogenesis of day 10.5 rat embryos cultured for 2 days in whole rat serum containing 0.1, 0.5, or 2.5 vol % acetone. Embryos cultured in medium containing 2.5% of the agent failed to grow, did not differentiate, and died during the culture period. In embryos exposed to 0.5% acetone, the increase in yolk sac diameter was significantly reduced even though yolk sac protein and DNA were not affected. No in vivo mammalian studies were found for acetone.

40.3.1.4 Other Toxicologic Effects

40.3.1.4.1 Short-term Toxicity

The oral LD_{50} of acetone for mice is reported to be 3000 mg/kg (51), while the oral LD_{50} for rats is listed as 9750 mg/kg (51). Acetone primarily acts as an irritant and as a depressant of the CNS. Common signs of acetone toxicity include eczema, conjunctivitis and corneal erosion, pharyngitis and bronchitis, CNS depression, weakness and narcosis (59).

Early studies revealed that acetone produces depression of the respiratory and vasomotor centers in a variety of experimental animals (1029). Specht et al. (1041) exposed guinea pigs to 20,000 ppm of acetone. Irritation of the mucous membranes, narcosis, CNS depression and respiratory dysfunction were observed. A decrease of 30 breaths/minute and 50 heartbeats/minute were recorded at 4800 ppm, while a decrease in body temperature 4°C below normal occurred at 10,800 ppm. Histological examination revealed congestion of the lungs and kidney as well as hemorrhaging in the pulp of the spleen.

Goldberg et al. (1051) studied the behavioral effects of acetone on rats. Rats were trained to climb a pole within two seconds of a stimulus. A delay of more than 6 seconds was considered to be a significant change in behavior. Rats were then exposed to 3000, 6000, 12,000, or 16,000 ppm of acetone vapor for 4 hours/day, 5 days/week for two weeks. Performance of each rat was tested before and after each exposure. Acetone at concentrations of 6000 ppm or above resulted in a significant modification of the avoidance and escape behavior pattern. Several rats exposed to the 12,000 or the 16,000 ppm level initially developed muscular incoordination after exposure, however, no signs of incoordination were reported on subsequent exposures.

Due to the narcotic effect of acetone at high concentrations, Geller et al. (1012) attempted to determine if exposure to half the TLV concentration would produce similar low level effects on CNS function. A match-to-sample discrimination task was used to measure the behavioral response of baboons exposed to acetone compared with performance under normal conditions. Baboons subjected to 500 ppm acetone, 6 hours/day for 7 days exhibited a marked change in the number of extra responses made during exposure. An increase in response time was also demonstrated. Geller concluded that these effects were the result of a slight narcosis associated with acetone exposure at very low levels.

Lo et al. (3400) investigated the effects of acetone on N-(3,5-dichlorophenyl)succinimide-induced (NDPS) nephrotoxicity in male Fischer 344 rats. The animals were given 1, 5, or 10 μmol/kg acetone orally, followed 16 hr later by a single intraperitoneal injection of NDPS (0.2 or 0.4 μmol/kg). It was found that 1 or 5 μmol/kg acetone did not alter 0.2 μmol/kg NDPS-induced renal effects, while 10

μmol/kg acetone pretreatment attenuated 0.4 μmol/kg NDPS-induced increases in blood urea nitrogen concentration and kidney weight, and had no effect on 0.4 μmol/kg NDPS-induced changes in urine volume or content or on renal morphology. It was suggested that acetone weakly attenuated NDPS-induced nephrotoxicity.

Freeman and Hayes (3228) investigated the nature and mechanism of a toxicologic interaction between acetonitrile and acetone. In oral dose-response studies in female Sprague-Dawley-derived rats, the LD_{50} values for acetone and acetonitrile alone were found to be 5800 and 4050 mg/kg, respectively; the LD_{50} for the 1:1 (W/W) mixture of acetone and acetonitrile was 1160 mg/kg. Further experiments led to the conclusion that acetone potentiated acetonitrile toxicity via a biphasic effect on the metabolism of acetonitrile to cyanide (that is, an initial inhibition followed by a delayed stimulation of this metabolism).

40.3.1.4.2 Chronic Toxicity

Male ICR mice and albino rats were exposed to 19,000 ppm of acetone vapor 3 hours/day, 5 days/week for 8 weeks. Animals were sacrificed after 2, 4, 8, and 10 weeks. Histopathological examination of tissues did not reveal any organ damage. Depression of body weight gain was the only adverse effect of chronic acetone exposure indicated (1078).

Rengstorff (1045) investigated the effects of dermal or subcutaneous injections of acetone in albino guinea pigs. Animals were exposed cutaneously to 0.5 ml of acetone or were injected subcutaneous on the back with either a 5% or 50% acetone in saline solution. Animals were dosed 3 times a week for 3 weeks. Examinations were conducted 60 to 90 days after the first application or injection, and every thirty days thereafter for 6 months. Two of the twelve animals cutaneously exposed to undiluted acetone developed bilateral cataracts involving the entire periphery of the lens. Two out of four animals treated subcutaneously with the 50% solution and five out of twelve animals injected with the 5% acetone solution developed cataracts. Three of the animals in this 5% acetone solution treatment group showed a disappearance of lens damage as time elapsed, and by 6 months, lenses had returned to normal.

Due to the unexpected effect acetone had on the eyes of guinea pigs, Rengstorff dropped 1.0 ml of acetone on the dorsal thorax area of 8 albino guinea pigs and 8 New Zealand white rabbits two times a day, 5 days a week for 4 or 8 weeks. Saline was substituted for acetone in the control group in addition to 4 guinea pigs receiving no treatment. Examinations were made each week for 8 weeks and then every other week for the remainder of the 6 month period. Two of the 8 guinea pigs developed bilateral cataracts in the 8-week-treatment group. No lens abnormalities were observed in any of the experimental or control rabbits or in the control guinea pigs. Histological appearance of the acetone-treated eyes showed advanced lens lesions suggesting a progressive sclerotic change (1045). Rengstorff theorized that the mechanism which induces the crystalline lens opacities in acetone-treated guinea pigs

is the same metabolic mechanism involved in the pathology of diabetic cataracts, and is related to the accumulation of ketone bodies such as acetone in the aqueous humor.

40.3.2 Human and Epidemiologic Studies

40.3.2.1 Short-term Toxicologic Effects

Exposure to acetone vapor usually results in irritation to the eyes, nose and throat. Dizziness and narcosis occur with continued exposure.

Ross (1044) reported an incident of acute acetone intoxication in workmen cleaning out a 12-foot-deep pit. Tanks of acetone and 1,1,1-trichloroethane were stored next to the pit. Two men descended into the pit and filled water into 2 buckets which were hoisted up and out of the pit by two men at the top of the ladder. All four men noticed a sickly sweet odor while working. One man working in the pit felt throat irritation, weakness in the legs and had a severe headache. The other man in the pit experienced eye irritation and felt "drunk" just before noontime. After a one hour lunch break, this man descended into the pit, filled one bucket of water and fainted. Four men came to assist the unconscious man out of the pit. All immediately experienced eye irritation and dizziness. Urine samples of the 8 men ranged from 4.6-7.2 mg acetone/100 ml urine. Samples taken 7 days later showed acetone levels had returned to normal, ranging between 0.39-1.29 mg acetone/100 ml urine. Air samples taken 3 hours after the men were taken to the hospital revealed acetone levels in excess of 12,000 ppm and 1,1,1-trichloroethane levels of up to 50 ppm.

Matsushita et al. (1052) conducted an inhalation study using five groups of five male volunteers. Each group was subjected to 0, 100, 200, 500, or 1000 ppm of acetone for 6 hours. Most of the subjects in the 500 and 1000 ppm groups experienced irritation of the nose, eyes, throat and trachea. Men in these groups also complained of tension, general weakness, heavy eyes or lack of energy the following morning. The 250 ppm group experienced similar complaints, but to a lesser extent. No complaints were reported in the 100 ppm group.

Lupulescu et al. (1053) studied the effect of 1 ml of acetone when applied to the skin of 7 volunteers for 90 minutes. Mild edema and hyperemia were the only clinical signs observed. Electron microscopic examination of the affected skin revealed cell damage and cytoarchitectural disorganization in the stratum corneum. These findings indicate that acetone affects the organization and cell homeostasis of the upper layers of human skin.

Ingestion of 200 ml of acetone resulted in a stuporous condition with flushed cheeks, shallow breathing, and a pulse rate of 108. The throat was red and swollen and erosion was observed on the soft palate and around the entrance to the esophagus. The individual lapsed into a coma shortly after admission to the hospital.

Supportive therapy was given and the individual regained consciousness 12 hours later. Pain and an increased sensitivity in the legs and hips developed 6 days later and persisted for two months. Four weeks after the initial ingestion of acetone, the subject had an increased fluid intake along with an increased urine output. An oral glucose tolerance test gave values in the diabetic range, but levels gradually returned to normal over a 2.5 months period (1048). Recent work by Casazza et al. (1049) indicates that hepatocytes isolated from chronic acetone-fed rats are capable of converting acetone to glucose in vitro.

40.3.2.2 Chronic Toxicologic Effects

Chronic exposure to acetone may cause harmful effects resulting in hyperemia of the conjunctiva and pharynx, lung irritation and rough breathing, dizziness, headaches, insomnia, and epigastric pain (1055).

Vigliani and Zurlo (1050) studied the health of factory workers exposed to 1000 ppm of acetone, 3 hours/day for 7-15 years. All the workers examined had inflamed respiratory tracts, stomachs and duodenums. They also reportedly experienced dizzy spells and loss of strength.

40.3.3 Levels of Concern

No water quality criteria or standards have been established for acetone. The OSHA (3539) standard is 750 ppm averaged over an 8-hour work-shift and 1000 ppm for a 15-min exposure. The ACGIH (3005) recommend a threshold limit value of 750 ppm, with a short-term exposure limit of 1000 ppm. The USEPA has proposed an Oral Reference Dose of 0.1 mg/kg/day (3744).

40.3.4 Hazard Assessment

Acetone is generally considered to be among the least toxic solvents used in industry (12). Human exposure to vapor concentrations of 250-1000 ppm results in irritation of eyes, nose and throat (1052); higher vapor concentrations can produce depression of the central nervous system and narcosis (59, 1044). Oral LD_{50} values for acetone range from 3 to 10 g/kg in rodents (51). Human ingestion of 200 mL of acetone induced gastroenteritis, narcosis and possible renal injury (1048).

Animal studies indicate signs of slight narcosis in baboons exposed to 500 ppm acetone (1012). Chronic dermal application of acetone resulted in the development of reversible cataracts in guinea pigs but not rabbits (1045); these cataracts may be related to the same metabolic mechanism associated with cataract formation in diabetics, i.e., the rise in ketone bodies in the eye.

Carcinogenicity tests are limited to a single skin-painting experiment of inadequate duration in mice (1043). No indications of tumor production were observed and there are no reports in the literature to implicate acetone as a

carcinogen. Negative results were obtained in Ames mutagenicity tests (1017, 1054) and in an in vivo micronucleus test (3055). Acetone was shown to induce aneuploidy in yeast (1011). Injection of acetone directly into the yolk sacs of chick eggs produced no evidence of terata (1042).

The widespread use of acetone in industrial applications without indications of serious health effects suggest low level acetone exposure does not pose a significant health hazard.

40.4 SAMPLING AND ANALYSIS CONSIDERATIONS

Determination of the concentrations of acetone in soil and water requires collection of a representative field sample and laboratory analysis. Due to the volatility of acetone, care is required to prevent losses during sample collection and storage. Soil and water samples are collected in airtight containers with no headspace; analysis should be completed within 14 days of sampling. However, recent studies (3430) show large losses of volatiles from soil handling. At the present, the best procedure is to collect the needed sample in an EPA VOA vial, seal with a foil-lined septum cap, and analyze the entire contents in the vial using a modified purge and trap apparatus. In addition to the targeted samples, quality assurance samples such as field blanks, duplicates, and spiked matrices should be included in the analytical program.

Acetone is not included among the EPA-designated priority pollutants. However, EPA Methods 624, 1624 (65), 8015, and 8240 (63) should be appropriate methods of choice for the analysis of acetone in aqueous samples. An inert gas is bubbled through the aqueous sample in a purging chamber at ambient temperature, transferring the acetone from the aqueous phase to the vapor phase and onto a sorbent trap. The trap is then heated and backflushed to desorb the acetone and transfer it into a gas chromatographic (GC) column. The GC column is programmed to separate the volatile organics; acetone is then detected with a flame ionization detector (Method 8015) or a mass spectrometer (Methods 624, 1624, and 824). Direct injection may also be used for samples containing elevated concentrations.

The EPA procedures recommended for analysis of chemical such as acetone in soil and waste samples, Methods 8015 and 8240 (63), differ from the aqueous procedures primarily in the method by which the analyte is introduced into the GC. The recommended method for low level samples (>1 mg/kg) involves dispersing the soil or waste sample in water and purging in a heated purge and trap device. Other sample introduction techniques include direct injection and a headspace method.

Acetone detection limits for most of the methods were not determined but would be in the range of 1-100 μg/L for aqueous samples and 1 μg/g for non-aqueous samples.

Aqueous Detection Limit	Non-Aqueous Detection Limit
100 μg/L (Method 8240)	100 μg/kg (Method 8240)
50 μg/L (Method 1624)	

40.5 REFERENCES

Note: The nonsequential numbers of the references reflect the order of references as they appear in the master bibliography.

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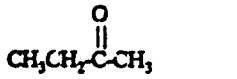
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COMMON SYNONYMS:	CAS REG.NO.: FORMULA:	AIR W/V CONVERSION FACTOR at 25°C (59)
2-Butanone Ethyl methyl ketone MEK Methyl acetone Methyl ethyl ketone	78-93-3 C_4H_8O NIOSH NO: EL6475000 STRUCTURE: 	2.94 mg/m³ ≈ 1 ppm; 0.340 ppm ≈ 1 mg/m³ MOLECULAR WEIGHT: 72.10

REACTIVITY	Reactions of ketones such as methyl ethyl ketone with cyanides, mercaptans, or other organic sulfides typically produce heat, while those with alkali or alkaline earth elemental metals, nitrides or strong reducing agents evolve heat and flammable gases. Reactions with oxidizing mineral acids or other strong oxidizing agents may generate heat and fire. Those with azo or diazo compounds or hydrazines may generate heat and usually innocuous gases. Reactions with organic peroxides or hydroperoxides typically result in explosions. Various manufacturers list oxidizing agents, chlorinated hydrocarbons in the presence of alkalies, alkanolamines, amines, pyridines, ammonia, caustics, inorganic acids, isocyanates, and halogens as incompatible materials (505, 507, 511).

PHYSICO-CHEMICAL DATA	• Physical State: Liquid (at 20°C)	(23)
	• Color: Colorless	(23)
	• Odor: Acetone-like	(23)
	• Odor Threshold: 5.400 to 10.000 ppm	(2,384)
	• Density: 0.8050 g/mL (at 20°C)	(14)
	• Freeze/Melt Point: -86.40°C	(23)
	• Boiling Point: 79.60°C	(14)
	• Flash Point: -6.70 to- 3.90°C (closed cup), -5.6 to -1.1°C (open cup)	(60,507,514)
	• Flammable Limits: 1.70 to 12.00% by volume	(51,60,506) (507)

PHYSICO-CHEMICAL DATA (Cont.)	• Autoignition Temp.: 404.0 or 516.0°C	(51,60,506) (510)
	• Vapor Pressure: 7.06E+01 mm Hg (at 20°C)	(59)
	• Satd. Conc. in Air: 2.7907E+05 mg/m³ (at 20°C)	(1219)
	• Solubility in Water: 3.53E+05 mg/L (at 10°C)	(67)
	• Viscosity: 0.400 cp (at 25°C)	(23)
	• Surface Tension: No data	
	• Log (Octanol-Water Partition Coeff.): 0.29	(29)
	• Soil Adsorp. Coeff.: 9.40E-01	(611)
	• Henry's Law Const.: 4.35E-05 atm · m³/mol (at 20°C)	(1138)
	• Bioconc. Factor: 9.00E-02, 1.86	(659,1137)

PERSISTENCE IN THE SOIL-WATER SYSTEM	Methyl ethyl ketone is expected to migrate in the soil/ground-water system with very little retardation. Volatilization from near-surface soils may occur; however, vapor concentrations in soil are expected to be very low whenever water is present. Biodegradation of methyl ethyl ketone has been demonstrated and persistence in environments with active microbial populations is not expected.

PATHWAYS OF EXPOSURE	The primary pathway of concern from a soil/groundwater system is the migration of methyl ethyl ketone to groundwater drinking water supplies. Inhalation may be important in some situations. Bioaccumulation of methyl ethyl ketone is not likely to be an important exposure pathway.

HEALTH HAZARD DATA	Signs and Symptoms of Short-term Human Exposure: (13) Eye, nose and throat irritation are usually the first symptoms to appear in methyl ethyl ketone exposure. At high concentrations, CNS depression and narcosis along with congestion of the lungs, liver and kidneys are observed. Acute Toxicity Studies: INHALATION: LC_{50} 40,000 mg/m³ · 2 hr — Mouse (47) LC_{50} 23,500 mg/m³ · 8 hr — Rat (3504) ORAL: LD_{50} 2737 mg/kg — Rat (47) LD_{50} 4050 mg/kg — Mouse (3504) SKIN: LD_{50} 13,000 mg/kg — Rabbit (47) LD_{50} 6480 mg/kg — Rabbit (3504) Long-Term Effects: Dermatitis Pregnancy/Neonate Data: Not teratogenic in rats; slightly fetotoxic at dose levels (3000 ppm) producing slight maternal toxicity Genotoxicity Data: Limited data are conflicting Carcinogenicity Classification: IARC - No data NTP - No data EPA - Group D (not classifiable as to human carcinogenicity)

HANDLING PRECAUTIONS (54)	Handle chemical only with adequate ventilation • Vapor concentration of 200 1000 ppm: chemical cartridge respirator with organic vapor cartridge and full facepiece • 1000-30,000 ppm: NIOSH approved respirator with organic vapor canister, any supplied air respirator or self-contained breathing apparatus with full facepiece • Wear appropriate clothing to prevent repeated or prolonged skin contact with the liquid • Chemical goggles if there is probability of eye contact. Rubber gloves.

ENVIRONMENTAL AND OCCUPATIONAL STANDARDS AND CRITERIA

AIR EXPOSURE LIMITS:

Standards
- OSHA PEL (8-hr TWA): 200 ppm; STEL (15-min): 300 ppm
- AFOSH PEL (8-hr TWA): 200 ppm; STEL (15-min): 200 ppm

Criteria
- NIOSH IDLH (30-min): 3000 ppm
- NIOSH REL (10-HR TWA): 200 ppm
- ACGIH TLV(R) (8-hr TWA): 200 ppm
- ACGIH STEL (15-min): 300 ppm

WATER EXPOSURE LIMITS:

Drinking Water Standards
None established

EPA Health Advisories and Cancer Risk Levels (3977)
The EPA has developed the following Health Advisories which provide specific advice on the levels of contaminants in drinking water at which adverse health effects would not be anticipated.

- 1-day (child): 80 mg/L
- 10-day (child): 8 mg/L
- longer-term (child): 3 mg/L
- longer-term (adult): 9 mg/L
- lifetime (adult): 0.2 mg/L

WHO Drinking Water Guideline
No information available

ENVIRONMENTAL AND OCCUPATIONAL STANDARDS AND CRITERIA (Cont.)

WATER EXPOSURE LIMITS:

EPA Ambient Water Quality Criteria

- Human Health (355)
  - No criterion established; methyl ethyl ketone is not a priority pollutant.
- Aquatic Life (355)
  - No criterion established; methyl ethyl ketone is not a priority pollutant.

REFERENCE DOSES:

ORAL: 5.000E+01 µg/kg/day (3744)

REGULATORY STATUS (as of 01-MAR-89)

Promulgated Regulations

- Federal Programs

Safe Drinking Water Act (SDWA)

In states with an approved Underground Injection Control program, a permit is required for the injection of methyl ethyl ketone-containing wastes designated as hazardous under RCRA (295).

Resource Conservation and Recovery Act (RCRA)

Methyl ethyl ketone is identified as a toxic, ignitable hazardous waste (U159) and listed as a hazardous waste constituent (3783, 3784). Non-specific sources of methyl ethyl ketone-containing waste that contain at least 10% methyl ethyl ketone are solvent use (or recovery) activities (987). Wastestreams from the ink formulation industry contain methyl ethyl ketone and are listed as specific sources of hazardous waste (3774, 3765). Methyl ethyl ketone is subject to land disposal restrictions when its concentration as a hazardous constituent of certain wastewaters exceeds designated levels (3785). Effective November 8, 1988, spent solvent wastes containing methyl ethyl ketone are prohibited from land disposal. Certain variances exist until May, 1990 for some wastewaters, nonwastewaters and contaminated soils for which Best Demonstrated Available Technology (BDAT) treatment standards have not been promulgated by EPA (3786).

Methyl ethyl ketone is included on EPA's ground-water monitoring list. EPA requires that all hazardous waste treatment, storage, and disposal facilities monitor their ground-water for chemicals on this list when suspected contamination is first detected and annually thereafter (3775).

Toxic Substances Control Act (TSCA)
Manufacturers, processors or distributors of methyl ethyl ketone must report production, usage and disposal information to EPA. They, as well as others who possess health and safety studies on methyl ethyl ketone, must submit them to EPA (334, 3789).

Comprehensive Environmental Response Compensation and Liability Act (CERCLA)
Methyl ethyl ketone is designated a hazardous substance under CERCLA. It has a reportable quantity (RQ) limit of 2270 kg. Reportable quantities have also been issued for RCRA hazardous waste streams containing methyl ethyl ketone but these depend upon the concentrations of the chemicals in the waste stream (3766). Under SARA Title III Section 313, manufacturers, processors, importers, and users of methyl ethyl ketone must report annually to EPA and state officials their releases of this chemical to the environment (3787)

Federal Insecticide, Fungicide and Rodenticide Act (FIFRA)
Methyl ethyl ketone is exempt from a tolerance requirement when used as a surfactant in pesticide formulations applied to growing crops (315).

Marine Protection Research and Sanctuaries Act (MPRSA)
Ocean dumping of organohalogen compounds as well as the dumping of known or suspected carcinogens, mutagens or teratogens is prohibited except when they are present as trace contaminants. Permit applicants are exempt from these regulations if they can demonstrate that such chemical constituents are non-toxic and non-bioaccumulative in the marine environment or are rapidly rendered harmless by physical, chemical or biological processes in the sea (309).

Occupational Safety and Health Act (OSHA)
Employee exposure to methyl ethyl ketone shall not exceed an 8-hour time-weighted average (TWA) of 200 ppm, and a 15-minute short-term exposure limit (STEL) of 300 ppm (3539).

Hazardous Materials Transportation Act (HMTA)
The Department of Transportation has designated methyl ethyl ketone as a hazardous material with a reportable quantity of 2270 kg, subject to requirements for packaging, labeling and transportation (3180).

Food, Drug and Cosmetic Act (FDCA)
Methyl ethyl ketone is approved for use as an indirect food additive only as component of adhesives (3209).

- State Water Programs

ALL STATES
All states have adopted EPA Ambient Water Quality Criteria and NPDWRs (see Water Exposure Limits section) as their promulgated state regulations, either by narrative reference or by relisting the specific numeric criteria. These states have promulgated additional or more stringent criteria:

CONNECTICUT
Connecticut has an action level of 1000 μg/L for methyl ethyl ketone in drinking water (3138).

KANSAS
Kansas has an action level of 170 μg/L for ground-water (3213).

NEW HAMPSHIRE
New Hampshire has set an enforceable Toxic Contaminant Level (TCL) for methyl ethyl ketone in drinking water of 1 mg/L for a 10-day exposure (assumes a child weighing 10 kg who drinks one liter of water per day) (3710).

NEW YORK
New York has an MCL of 50 μg/L for methyl ethyl ketone in drinking water (3501).

OKLAHOMA
Oklahoma has a water quality criterion of 0.8 μg/L for ground-water (3534).

SOUTH DAKOTA
South Dakota requires methyl ethyl ketone to be nondetectable, using designated test methods, in ground-water (3682).

VERMONT
Vermont has a preventive action limit of 85 μg/L and an enforcement standard of 170 μg/L for methyl ethyl ketone in ground-water (3682).

Proposed Regulations

- Federal Programs

  Resource Conservation and Recovery Act (RCRA)

  EPA has proposed that solid wastes be listed as hazardous because they exhibit the characteristic defined as EP toxicity when the TCLP extract concentration is equal to or greater than 7.2 mg/L methyl ethyl ketone. Final promulgation of this Toxicity Characteristic Rule is scheduled for June, 1989 (1565).

- State Water Programs

  MOST STATES

  Most states are in the process of revising their programs and propcsing changes in their regulations which will follow EPA's changes when they become final. Contact with the state officer is advised. Changes are projected for 1989-90 (3683).

  MINNESOTA

  Minnesota has proposed a Recommended Allowable Limit (RAL) of 170 µg/L for methyl ethyl ketone in drinking water (3451). Minnesota has also proposed a Sensitive Acute Limit (SAL) of 468 µg/L for designated surface waters, and a chronic criterion of 170 µg/L for designated surface and ground-waters for the protection of human health (3452).

EEC Directives

Directive on Marketing and Use of Dangerous Substances (541)

Methyl ethyl ketone may not be used in ornamental objects intended to produce light or color effects by means of different phases.

Directive Relating to the Classification Packaging and Labeiing of Dangerous Preparations (Solvents) (544)

Methyl ethyl ketone is listed as a Class II/a harmful substance and is subject to packaging and labeling regulations.

Directive on the Classification, Packaging and Labeling of Dangerous Substances (778)

Methyl ethyl ketone is classified as a flammable substance and is subject to packaging and labeling regulations. This substance may contain a stabilizer. If the stabilizer changes the dangerous properties of the substances a label should be provided. The designation, cas-number, classification and labelling of this substance is replaced with Annex I of EEC-88-490, July 22, 1988.

EEC Directives - Proposed
Resolution on a Revised List of Second-Category Pollutants
(545)
Methyl ethyl ketone is one of the second-category pollutants to be studied by the Commission in the programme of action of the European Communities on Environment in order to reduce pollution and nuisances in the air and water. Risk to human health and the environment, limits of pollutant levels in the environment, and determination of quality standards to be applied will be assessed.

41.1 MAJOR USES

Methyl ethyl ketone is used primarily as a solvent. The coating industry uses methyl ethyl ketone extensively, accounting for 61% of its production, to manufacture gums, resins and nitrocellulose. Approximately 18% of the methyl ethyl ketone produced is used to make cements and adhesives. Other manufacturers utilize methyl ethyl ketone to produce printing ink, cleaning fluids, smokeless powders and wax (200, 59, 67).

41.2 ENVIRONMENTAL FATE AND EXPOSURE PATHWAYS

41.2.1 Transport in Soil/Ground-water Systems

41.2.1.1 Overview

Methyl ethyl ketone is expected to be fairly mobile in the soil/ground-water system when present at low concentrations or as a separate organic phase (resulting from a spill of significant quantities of the chemical). In general, transport pathways can be assessed by using an equilibrium partitioning model, as shown in Table 41-1. These calculations predict the partitioning of low soil concentrations of methyl ethyl ketone among soil particles, soil water and soil air. Portions of methyl ethyl ketone associated with the water and air phases of the soil have higher mobility than the adsorbed portion.

Estimates for the unsaturated topsoil model indicate that only 15.2% of the methyl ethyl ketone is expected to be sorbed onto soil particles. Approximately 84% is expected to partition to the soil-water phase, and is thus available to migrate by bulk transport (e.g., the downward movement of infiltrating water), dispersion and diffusion. For the small portion of methyl ethyl ketone in the gaseous phase of the soil (0.5%), diffusion through the soil-air pores up to the ground surface, and subsequent removal by wind, may be a significant loss pathway.

In saturated, deep soils (containing no soil air and negligible soil organic carbon), almost all of the methyl ethyl ketone (99.6%) is predicted to be present in the soil-water phase (Table 41-1) and available for transport with flowing ground water. Sorption onto deep soils (0.4%) is not expected to be significant. Overall, ground water underlying methyl ethyl ketone-contaminated soils with low organic content is expected to be vulnerable to contamination.

TABLE 41-1
EQUILIBRIUM PARTITIONING CALCULATIONS FOR METHYL ETHYL KETONE IN MODEL ENVIRONMENTS[a]

Soil Environment	Estimated Percent of Total Mass of Chemical in Each Compartment		
	Soil	Soil-Water	Soil-Air
Unsaturated topsoil at 25°C[b,c]	15.2	84.3	0.5
Saturated deep soil[d]	0.4	99.6	-

a) Calculations based on Mackay's equilibrium partitioning model (34, 35, 36); see Introduction in Volume 1 for description of model and environmental conditions chosen to represent an unsaturated topsoil and saturated deep soil. Calculated percentages should be considered as rough estimates and used only for general guidance.
b) Used estimated soil sorption coefficient: K_{oc} = 0.94 (611).
c) Henry's law constant taken as 4.35E-05 atm · m³/mol at 25°C (74).
d) Used sorption coefficient K_p = 0.001 K_{oc}.

41.2.1.2 Sorption on Soils

The mobility of methyl ethyl ketone in the soil/ground-water system (and its eventual migration into aquifers) is governed by the extent of its sorption on soil particles. In general, sorption on soils is expected to:

- increase with increasing soil organic matter content;
- increase slightly with decreasing temperature;
- increase moderately with increasing salinity of the soil water; and
- decrease moderately with increasing dissolved organic matter in the soil water.

No information specific to the adsorption of methyl ethyl ketone in the environment was available. Methyl ethyl ketone is highly soluble in water and its low values for log K_{ow} and K_{oc} suggest that sorption to soils/sediments does not contribute significantly to its environmental fate. Methyl ethyl ketone in the soil/ground-water system is expected to be only slightly less mobile than acetone, which was reported to migrate freely with little or no retardation.

41.2.1.3 Volatilization from Soils

Transport of methyl ethyl ketone vapors through the air-filled pores of unsaturated soils may occur in near-surface soils. However, modeling results suggest that a very small fraction of the methyl ethyl ketone loadings will be present in the soil-air phase.

In general, important soil and environmental properties influencing the rate of volatilization include soil porosity, temperature, convection currents and barometric pressure changes; important physico-chemical properties include the Henry's law constant, the vapor-soil sorption coefficient, and to a lesser extent, the vapor phase diffusion coefficient (31).

The Henry's law constant (H), which provides an indication of a chemical's tendency to volatilize from solution, is expected to increase significantly with increasing temperature. Moderate increases in H have also been observed with increasing salinity and the presence of other organic compounds (18). These results suggest that the presence of other materials may significantly affect the volatilization of methyl ethyl ketone, particularly from surface soils. No information was available for the two other physicochemical properties influencing volatilization, i.e., the vapor-soil sorption coefficient and the vapor phase diffusion coefficient.

Experimental mass transfer coefficients (25°C) were determined for methyl ethyl ketone at several depths and mixing rates (1121). Volatilization half-lives calculated from the mass transfer coefficients ranged from 1.05 days for high mixing (2020 rpm) of a 15 cm aqueous solution to 2.25 days for low mixing (557 rpm) of a 20 cm aqueous solution. Lande et al. (1137) calculated an approximate half-life of 138 hours (5.75 days) for the evaporation (20°C) of methyl ethyl ketone from aqueous solution. It can be expected that the rate of volatilization may vary for aqueous environmental systems.

The significance of methyl ethyl ketone volatilization in the environment is not documented; data on volatilization from soils, in particular, are not available. Since methyl ethyl ketone is not strongly adsorbed to soil, some volatilization at the surface may occur; however, the ability of methyl ethyl ketone to be transported with soil water is significant. Furthermore, methyl ethyl ketone has been reported in rainwater samples (1136) suggesting that, due to its high water solubility, any methyl ethyl ketone lost due to volatilization may be washed out of the atmosphere and returned to the soil/water system.

41.2.2 Transformation Processes in Soil/Ground-water Systems

No information on the hydrolysis of methyl ethyl ketone in the soil/ground-water system was available; under normal environmental conditions, hydrolysis is not expected to occur at a rate competitive with volatilization or biodegradation. The portion of methyl ethyl ketone that has been released from the soil into the air will

either return to the soil via atmospheric washout or eventually undergo photochemical oxidation.

Methyl ethyl ketone is expected to be susceptible to extensive microbial biodegradation in pure cultures, mixed cultures, and activated sludge systems (1137). Several authors (1132, 1133) have reported the biodegradation of methyl ethyl ketone by microbes grown on propane, or by soil bacteria grown on C_1-C_3 aliphatic hydrocarbons; oxidation was observed even where methyl ethyl ketone was unable to support growth of the organism. Methyl ethyl ketone degradation by one of four tested yeast cultures was also reported (1131).

After five days of incubation, degradation of methyl ethyl ketone, as determined by BOD_5 tests with acclimated sewage seed or microbes from polluted waters, ranged from 48% to 88%; degradation after 20 days was observed to be 69% to 89% (880, 881, 882, 1127). Dojlido (1135) reported 100% degradation in 8 days for 200 mg/L methyl ethyl ketone and in 9 days for 400 mg/L. Chou et al. (1126) reported 77% utilization of methyl ethyl ketone in an anaerobic reactor; the same authors reported 100% anaerobic degradation by enriched methane cultures after an 8-day lag.

In actual soil/ground-water systems, the concentration of microorganisms capable of biodegrading methyl ethyl ketone may be low, and is expected to drop off sharply with increasing depth; prediction of biodegradation rates in the environment is not possible. However, in environments with sufficient microbial populations, methyl ethyl ketone is not expected to persist.

41.2.3 Primary Routes of Exposure from Soil/Ground-water Systems

The above discussion of fate pathways suggests that methyl ethyl ketone has a moderate volatility, is very weakly adsorbed to soil, and has no significant potential for bioaccumulation. This compound may volatilize from the soil surface, but that portion not removed by volatilization is likely to be mobile in ground-water. These fate characteristics suggest several potential exposure pathways.

Volatilization of methyl ethyl ketone from a disposal site could result in inhalation exposure to workers or residents in the area. In addition, the potential for ground-water contamination is high, particularly in sandy soils. It has been detected in ground water associated with hazardous waste sites. Mitre (83) reported that methyl ethyl ketone has been found at 10 of the 546 National Priority List (NPL) sites. It was detected at 4 sites in ground water, 4 in surface water, and 4 in air. However, it may not be commonly analyzed for at NPL sites as it is not a priority pollutant. These data, as well as the properties of methyl ethyl ketone, suggest that drinking water exposure from ground-water contamination is likely to be its primary route of exposure from soil/ground-water systems.

The movement of methyl ethyl ketone in ground water may result in discharge to surface water. As a result, ingestion exposures may occur resulting from the use of

surface waters as drinking water supplies, and dermal exposures may result from the recreational use of surface waters. Such exposures are likely to be lower than those from drinking contaminated ground water due to biodegradation and/or volatilization of methyl ethyl ketone in surface water. Any pathways related to the uptake by aquatic organisms or domestic animals from surface waters are likely to be less significant than other sources of exposure due to the low BCF for methyl ethyl ketone.

41.2.4 Other Sources of Human Exposure

Methyl ethyl ketone is widely used as a industrial solvent, coating, and adhesive. As such, there are a number of sources of human exposure. Data, however, are somewhat lacking. For example, it is not commonly measured in drinking water.

The production and use of methyl ethyl ketone has led to its presence in the atmosphere. Brodzinksy and Singh (84) summarized air monitoring data for a number of pollutants. For methyl ethyl ketone, they reported 181 data points for urban/suburban areas. All results for these samples were less than the detection limit. In source-dominated areas, the median concentration reported was 0.19 $\mu g/m^3$ for 33 data points.

Dermal exposure is expected to be common due to the prevalence of methyl ethyl ketone as a solvent in various products. For example, two surveys were conducted in Japan on the solvent content of a variety of products. They found methyl ethyl ketone in 26% of the paints, 21% of the inks, 23% of the adhesives, 11% of the thinners, and 8% of the degreasers that were sampled. While most of these products are used in occupational settings, some may be used by consumers (1140, 1141).

The ketones are naturally occurring components of food. Lande et al. (1137) reviewed the literature and found methyl ethyl ketone in a wide variety of foods including cheese (0.3 ppm), milk (0.08 ppm), cream (0.2 ppm), bread, oranges and rum. This compound appears to be a common component of the diet although a total exposure from this source can not be evaluated without additional data (1137).

41.3 HUMAN HEALTH CONSIDERATIONS

41.3.1 Animal Studies

41.3.1.1 Carcinogenicity

No data were available with regard to the carcinogenic potential of methyl ethyl ketone.

41.3.1.2 Genotoxicity

Methyl ethyl ketone showed no evidence of genotoxicity when tested in TA102 and TA104 strains of Salmonella typhimurium (1001). It was shown to be marginally positive, at best, in a Chinese V79 hamster cell assay which indicates the ability of compounds to inhibit gap junction-mediated intercellular communication (1013). Zimmermann (1011), using the diploid yeast strain D61.M of Saccharomyces cerevisiae, found methyl ethyl ketone strongly induced mitotic aneuploidy (having more or less than the normal number of chromosomes). In an in vivo study, Basler (3055) tested solvents known to induce aneuploidy in yeast in a micronucleus assay in which male and female Chinese hamsters received 411 mg/kg methyl ethyl ketone intraperitoneally; there was no significant increase above controls in micronucleated polychromatic erythrocytes in the bone marrow cells of the treated animals.

41.3.1.3 Teratogenicity, Embryotoxicity and Reproductive Effects

Schwetz et al. (1003) exposed pregnant Sprague-Dawley rats to 1000 or 3000 ppm of methyl ethyl ketone vapor in a chamber for 7 hours a day on days 6 through 15 of gestation. No evidence of maternal toxicity was observed. A retardation of fetal development and a significant increase in the number of anomalous skeletons (19% vs. 0 in the control group) were observed at both the 1000 and 3000 ppm treatment levels. Examination of the litters of the dams exposed to 3000 ppm methyl ethyl ketone revealed 2 fetuses with acaudia (no tails) and imperforated anus, and 2 fetuses with brachygnathia (shortened lower jaw). Though these unusual anomalies were not statistically significant, Schwetz did note that they had never before been observed in control animals in the Sprague-Dawley strain in his laboratory.

Due to a lack of dose-related response in the previous experiment, Deacon et al. (1005, 3341) duplicated the study in order to determine the repeatability of the unusual anomalies observed by Schwetz. Experimental design was identical. Exposure to 3000 ppm methyl ethyl ketone produced a slight maternal toxicity as shown by a decreased maternal weight gain. Minor anomalies in fetal development included an extra lumbar rib and delayed ossification of the cervical centra which were noted by Deacon to occur at low incidence historically among control rats in his laboratory. The findings presented in this follow-up study indicate that methyl ethyl ketone produced a slight fetotoxic effect at the 3000 ppm exposure level, but no embryotoxic or teratogenic response in rats.

41.3.1.4 Other Toxicologic Effects

41.3.1.4.1 Short-term Toxicity

Acute exposure to methyl ethyl ketone generally results in irritation to the eyes, nose and throat, CNS depression, emphysema and congestion of the liver and kidneys. The oral LD_{50} range for rats is reported to be 2.7-3.6 g/kg (47, 13) while the reported

LC_{50} value in the mouse is a two-hour exposure to 40,000 mg/m³ methyl ethyl ketone (47).

Patty et al. (1028) describe the effects of airborne methyl ethyl ketone on guinea pigs at concentrations of 0.33, 1.0, 3.3 or 10.0% for up to 810 minutes. Signs of toxicity included irritation of the nose and eyes, incoordination, narcosis, gasping and death. Necropsy revealed emphysema, slight congestion of the brain and marked congestion of the systemic organs, particularly the lungs.

Exposure of guinea pigs to 10% methyl ethyl ketone vapor for 30 minutes resulted in opaque corneas. Examination eight days later showed that the eyes had returned to normal, indicating a reversibility of the damage (1028).

It has been well established that ketones as a class can cause narcosis at high concentrations (13, 1029). However, it is believed (1012) that ketones may also be capable of producing a modification of behavior or impairment of judgement at lower concentrations. Geller et al. (1012) evaluated the effect of low-level methyl ethyl ketone exposure on delayed match-to-sample tasks in the baboon. Four juvenile baboons were exposed to 100 ppm methyl ethyl ketone, 24 hours a day for 7 days. Accuracy of performance was minimally affected. However, extra responses during the delay period were recorded and the response time was significantly increased. These effects were considered to be an early manifestation of the incoordination and narcosis which are observed at much higher concentrations.

Tham et al. (1006) demonstrated that a component of the equilibrium system, the vestibulo-ocular reflex (VOR), was depressed in rats when methyl ethyl ketone was infused into the circulatory system at a rate of 70 μM/kg/minute for 60 minutes, resulting in blood levels of 100 ppm. Nystagmus (a rapid, involuntary movement of the eye ball) was induced by accelerated rotation to study vestibular function. Depression of the VOR is considered an early sign of intoxication prior to the onset of a general depression of the central nervous system.

41.3.1.4.2 Chronic Toxicity

Toxicity studies of methyl ethyl ketone are summarized by Yang (3855). In a subchronic inhalation study performed by Cavender et al. (1008, 3106), male and female Fischer 344 rats were exposed to 1250, 2500, or 5000 ppm methyl ethyl ketone in a chamber for 6 hours/day, 5 days/week for 90 days. The only clinical observation was a decrease in mean body weight in the group receiving 5000 ppm methyl ethyl ketone. Increases in liver weight and liver to body weight ratios were noted in both males and females in the 5000 ppm group and a depression of brain weight in females in the 5000 ppm group at necropsy. In the 5000 ppm group of female rats there was decreased serum glutamic-pyruvic transaminase activity, and increased alkaline phosphatase, potassium, and glucose values. Special neuropathological studies performed on tibial nerve fiber preparations, and Epon

sections of the sciatic nerve and the medulla, did not reveal any changes that could be attributed to methyl ethyl ketone.

Methyl ethyl ketone has been shown to shorten the latency period for the onset of neurotoxic effects of methyl butyl ketone and n-hexane in a number of species. Altenkirch (1002) studied the response of the nervous system to chronic repeated exposures of 10,000 ppm pure hexane, 10,000 ppm methyl ethyl ketone/n-hexane (ratio of 1:9) or 6000 ppm pure methyl ethyl ketone in rats. Motor neuropathy with giant swelling of axons in the peripheral and central nervous system, as well as severe potentiation of hexane neurotoxicity and shortened onset of morphological and clinical signs, developed in animals exposed to the methyl ethyl ketone/hexane mixture. Motor impairment of the methyl ethyl ketone/hexane treated rats varied from a waddling gait and eversion of hind limbs to quadriplegia. Methyl ethyl ketone alone did not produce neuropathy. Rats exposed to extremely high concentrations of pure methyl ethyl ketone (6000-10,000 ppm), however, developed severe bronchopneumonia and died.

The potentiation effect of methyl ethyl ketone on hexane-induced neuropathy has also been observed with methyl n-butyl ketone (1029, 1030). Rats intoxicated by continuous exposure to air containing methyl ethyl ketone and methyl n-butyl ketone vapor in a ratio of 1125:225 ppm developed clinical evidence of neuropathy after 25 days; rats inhaling 225 ppm methyl n-butyl ketone alone exhibited neuropathy after 66 days.

Methyl ethyl ketone potentiates the neurotoxic effects of methyl n-butyl ketone and hexane presumably by stimulating their metabolism to neurotoxic metabolites (1015). Both hexane and methyl n-butyl ketone share common products in their metabolic pathways, i.e., 2,5-hexanediol and 2,5-hexanedione. Hexanedione is believed to be the neurotoxic agent (1030, 1014). Administration of hexane and methyl ethyl ketone together results in a significant increase in the activity of mixed-function oxygenase enzymes in rats (1004) and the urinary excretion of 2,5-hexanedione is increased after administration of the methyl ethyl ketone/methyl n-butyl ketone mixture to rats (1002). Furthermore, administration of 2,5-hexanedione produced effects indistinguishable from hexane or methyl n-butyl ketone neurotoxicity (1014).

Ralston et al. (3579) studied the potentiation of 2,5-hexanedione neurotoxicity by methyl ethyl ketone in male F-344 rats. It was found that chronic oral administration of a combination of 2.2 μmol of methyl ethyl ketone and 2.2 μmol 2,2-hexanedione/kg/day, 5 days/week, resulted in more rapid onset of motor deficits than did chronic dosing with 2.2 μmol 2,5-hexanedione/kg/day alone. Following blood clearance and tissue uptake studies, it was suggested that the potentiation of hexacarbon neurotoxicity by methyl ethyl ketone was the result of the persistence of the neurotoxic metabolite in the blood and not the enhanced biotransformation of precursor hexacarbons to 2,5-hexanedione.

41.3.2 Human and Epidemiologic Studies

41.3.2.1 Short-term Toxicologic Effects

Berg et al. (1016) reported a case of retrobular neuritis in an 18-year-old male exposed to methyl ethyl ketone while removing paint in an enclosed area. Symptoms included a dull headache, mild vertigo and diminished vision in both eyes. Ophthalmic examination and testing 2 hours later revealed marked enlargment of the blind spot and superior arcuate-type defects in both eyes. Blood analysis showed the presence of methanol and formaldehyde. Thirty-six hours after exposure, vision returned to normal. Berg postulated that the patient had suffered optic nerve toxicity induced by methanol formed from the metabolism of methyl ethyl ketone.

Dick et al. (3171) studied the effects of acute exposure of 200 ppm of methyl ethyl ketone (and of toluene) on psychomotor performance in volunteers. Analysis of blood samples in twenty individuals exposed for 4 hr to methyl ethyl ketone showed concentrations of 3.1 ppm (S.D. = 1.2 ppm) and 3.7 ppm (S.D. = 1.6 ppm) after 2 hr and 4 hr exposure, respectively. There were no significant effects of methyl ethyl ketone on alertness or psychomotor function.

Munies and Wurster (1031) demonstrated that methyl ethyl ketone in contact with the skin resulted in a partial dehydration of the stratum corneum. Wahlberg (1009) showed that the spontaneous transient whitening of the skin caused by excessive exposure to methyl ethyl ketone is due to a change in structure and the removal of the skin lipids rather than by vasoconstriction.

41.3.2.2 Chronic Toxicologic Effects

Smith and Mayer (1032) investigated the effects of methyl ethyl ketone on a group of factory workers using methyl ethyl ketone as a solvent. Routes of exposure included both immersion of bare hands in the solvent and inhalation of 300-600 ppm. No duration of exposure was given. A number of workers developed severe dermatitis. Several workers also experienced numbness in the fingers, arms and legs. Symptoms disappeared when exposure to methyl ethyl ketone was discontinued.

Varigos and Nurse (3811) reported on contact urticaria caused by methyl ethyl ketone, in a 48 year-old painter, who had complained of severe skin irritation whenever the solvent touched his hands. An open test, using commercial grade MEK applied to the each forearm, showed that bright red areas appeared in 10 min; the reaction reached its maximum in 15 min after application, and gradually faded.

The potentiation of various hexacarbon neuropathies by methyl ethyl ketone is of particular interest in cases of solvent abuse. Altenkirch (1033) reported 25 cases of clinically severe toxic polyneuropathy in people addicted to inhaling methyl ethyl ketone-containing solvents. The peripheral motor defects took 2.5-3 years to become

apparent. The effects were considered to be due to an axonal transmission disorder which destroyed peripheral and central axons (0049).

Altenkirch (1004) also described what was known as the Berlin Poisoning Affair. In 1974, a solvent manufacturer changed its formulation to help stop inhalation abuse. The hexane content was reduced from 31 to 16% and 11% methyl ethyl ketone was added as a denaturant. An epidemic-like outbreak of 19 severe neuropathy syndromes occurred soon after the new formulation was available to the public. Neurological effects included considerable weight loss, muscular weakness affecting all four extremities or paralysis of all four extremities, extreme muscular atrophy, and respiratory disorders. In some cases, visual disturbances occurred and facial nerves were affected. Individuals examined up to 4 years after the incident still exhibited muscular atrophy, muscular weakness and sensory defects. This incident further supports findings that the neurotoxic properties of hexane can be potentiated by methyl ethyl ketone.

A female shoe-factory worker developed sensorimotor neuropathy after years of working with a glue containing 20% methyl ethyl ketone and 8% hexane (1007). The woman developed sensory and motor neuropathy in the lower limbs, and the absence of deep reflexes. This condition slowly regressed once exposure to the solvent mixture ceased.

41.3.3 Levels of Concern

The EPA (3977) has established a Lifetime Health Advisory for noncarcinogenic risk for exposure to methyl ethyl ketone of 0.2 mg/L in drinking water.

The OSHA (3539) standard is 200 ppm (590 mg/m^3) averaged over an 8-hour work-shift and for a 15-min exposure, 300 ppm (885 mg/m^3). The ACGIH (3005) recommends the same level. The threshold limit value was set to prevent injurious effects and minimize complaints about odor and irritation (46).

41.3.4 Hazard Assessment

Methyl ethyl ketone exhibits a low toxicity subsequent to acute and chronic exposures. The oral LD_{50} value for rats is in the 2.7 to 3.6 g/kg range (47, 13); the inhalation LC_{50} for mice for a two hour exposure is 40,000 mg/m^3 (47). At high concentrations (e.g., 10% in air), methyl ethyl ketone can induce narcosis (1028) but low level chronic exposure (2500 ppm for 90 days) produced no adverse effects in rats (1008).

Exposure to methyl ethyl ketone can produce local irritation of the eyes, upper respiratory tract and skin (1016, 1031, 1032). If splashed into the eyes, painful irritation and corneal injury may result (1028). Direct skin contact may produce

dermatitis and defat the skin (1032, 1009). Short-term human exposure to methyl ethyl ketone can produce headache, eye and throat irritation.

Studies in both humans and animals indicate that methyl ethyl ketone potentiates (i.e., shortens the time of onset) of peripheral neuropathy caused by either n-hexane or methyl n-butyl ketone. Methyl ethyl ketone itself does not induce peripheral neuropathy (1002, 1029, 1030).

The reproductive, mutagenic and carcinogenic activity of methyl ethyl ketone have not been thoroughly investigated and require further research. Female rats exposed via inhalation to over 1000 ppm methyl ethyl ketone resulted in fetotoxic effects. A low incidence of malformations was observed in one study (1003) but could not be duplicated using an identical experimental design (1005), suggesting that methyl ethyl ketone produces minor fetotoxic effects but is not a teratogen in rats.

Conflicting data are available regarding the mutagenicity of methyl ethyl ketone. Negative results were obtained in an Ames assay (1001), a marginally positive response at best in a Chinese V-79 hamster cell test (1013) and a strongly positive induction of aneuploidy in a yeast test (1011). Results were negative in an in vivo micronucleus test in Chinese hamster. There are no data available on the carcinogenic activity of methyl ethyl ketone.

41.4 SAMPLING AND ANALYSIS CONSIDERATIONS

Determination of the concentration of methyl ethyl ketone in soil and water requires collection of a representative field sample and laboratory analysis. Due to the volatility of methyl ethyl ketone, care is required to prevent losses during sample collection and storage. Soil and water samples are collected in airtight containers with no headspace; analysis should be completed within 14 days of sampling. However, recent studies (3430) show large losses of volatiles from soil handling. At the present, the best procedure is to collect the needed sample in an EPA VOA vial, seal with a foil-lined septum cap, and analyze the entire contents in the vial using a modified purge and trap apparatus. In addition to the targeted samples, quality assurance samples such as field blanks, duplicates, and spiked matrices should be included in the analytical program.

Methyl ethyl ketone is not included among the EPA-designated priority pollutants. However, EPA Methods 625, 1624 (65), 8015 and 8240 (63) would be appropriate methods of choice for the analysis of methyl ethyl ketone in aqueous samples. An inert gas is bubbled through the aqueous sample in a purging chamber at ambient temperature, transferring the methyl ketone from the aqueous phase to the vapor phase and onto a sorbent trap. The trap is then heated and backflushed to desorb the methyl ethyl ketone and transfer it onto a gas chromatographic (GC) column. The GC column is programmed to separate the volatile organics; methyl ethyl ketone is then detected with a flame ionization detector (Method 8015) or a

mass spectrometer (Methods 624, 1624, and 8240). Direct injection may also be used for samples containing elevated concentrations.

The EPA procedures recommended for methyl ethyl ketone analysis in soil and waste samples, Methods 8015 and 8240 (63), differ from the aqueous procedures primarily in the method by which the analyte is introduced into the GC. The recommended method for low level samples (<1 mg/kg) involves dispersing the soil or waste sample in water and purging in a heated purge and trap device. Other sample introduction techniques include direct injection and a headspace method.

Methyl ethyl ketone detection limits for most of the methods were not determined but would be in the range of 1-100 µg/L for aqueous samples and 1 µg/g for non-aqueous samples.

Aqueous Detection Limit	Non-Aqueous Detection Limit
100 µg/L (Method 8240) 50 µg/L (Method 1624)	100 µg/kg (Method 8240)

41.5 REFERENCES

Note: The nonsequential numbers of the references reflect the order of references as they appear in the master bibliography.

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COMMON SYNONYMS:	CAS REG.NO.: 109-86-4 FORMULA: $C_3H_8O_2$ NIOSH NO: KL5775000 STRUCTURE: $HO\text{-}CH_2\text{-}CH_2\text{-}O\text{-}CH_3$	AIR W/V CONVERSION FACTOR at 25°C (12) 3.11 mg/m³ ≈ 1 ppm; 0.322 ppm ≈ 1 mg/m³ MOLECULAR WEIGHT: 76.1
2-Methoxyethanol EGME Ektasolve em Ethylene glycol-methyl ether Ethylene glycol-monomethyl ether Jeffersol em Methyl cellosolve Methyl glycol		

REACTIVITY	The NFPA reports that contact of air with Methyl Cellosolve® forms peroxides that are highly explosive. NIOSH reports that contact with strong oxidizing agents may cause fires and/or explosions and that contact with strong caustics may cause decomposition. For compatibility classification purposes, Methyl Cellosolve® is considered to have attributes of both glycols and ethers. Reactions of glycols with non-oxidizing mineral acids typically generate heat, while those with oxidizing mineral acids, organic peroxides or hydro-peroxides, or other strong oxidizing agents may evolve heat and fire. Those with organic acids, isocyanates, or epoxides may initiate violent polymerization, while reactions with alkali or alkaline earth elemental metals or strong reducing agents may evolve heat, flammable gases and fire. Reactions with nitrides may produce heat, flammable gases, and an explosion, while those with azo or diazo compounds or hydrazines may generate heat and gases (38, 505, 511).

PHYSICO-CHEMICAL DATA	• Physical State: Liquid (at 20°C)	(45)
	• Color: Colorless	(45)
	• Odor: Mild, pleasant	(45)
	• Odor Threshold: 60.000 ppm	(2)
	• Density: 0.9746 g/mL (at 20°C)	(21)
	• Freeze/Melt Point: -85.00°C	(21)
	• Boiling Point: 124.00°C	(21)
	• Flash Point: 38.90 to 41.70°C (closed cup); 48.9°C (open cup)	(60,506,507)

PHYSICO-CHEMICAL DATA (Cont.)	• Flammable Limits: 2.50 to 19.80% by volume (1.8 to 14% at STP)	(38,60,506)
	• Autoignition Temp.: 285.0 to 288.3°C	(38,60,506)
	• Vapor Pressure: 6.00E+00 mm Hg (at 20°C)	(2)
	• Satd. Conc. in Air: 2.5000E+04 mg/m^3 (at 20°C)	(1219)
	• Solubility in Water: Miscible in all proportions	(38)
	• Viscosity: No data	
	• Surface Tension: 3.3000E+05 dyne/cm (at 20°C)	(60)
	• Log (Octanol-Water Partition Coeff.): -0.77	(29)
	• Soil Adsorp. Coeff.: 8.00E-02	(611)
	• Henry's Law Const.: 8.00E-09 $atm \cdot m^3/mol$, (estim) (at 20°C)	(966)
	• Bioconc. Factor: 8.00E-03 (estim)	(659)

PERSISTENCE IN THE SOIL-WATER SYSTEM	Methyl Cellosolve(rtm) is expected to be mobile in the soil/ground-water system due to its weak sorption on soils and high water solubility. Volatilization may occur at the surface but is expected to be of minimal importance whenever water is present. Data on biodegradation are inconclusive.

PATHWAYS OF EXPOSURE	The primary pathway of concern from a soil/ground-water drinking system is the migration of Methyl Cellosolve® to groundwater drinking water supplies, although no data confirm this. Inhalation or bioaccumulation of Methyl Cellosolve® from surface waters or soils are not likely to be important exposure pathways.

HEALTH HAZARD DATA	Signs and Symptoms of Short-term Human Exposure: (12, 38, 54) Acute exposure by inhalation to Methyl Cellosolve® generally results in narcosis, pulmonary edema and severe liver and kidney damage. Poisoning by ingestion resembles ethylene glycol toxicity, possibly resulting in renal failure and death. Acute Toxicity Studies: INHALATION: LC_{50} 1500 ppm · 7 hr — Rat (3504) ORAL: LD_{50} 2460 mg/kg — Rat (51) SKIN: LD_{50} 1280 mg/kg — Rabbit (51) Long-Term Effects: Hematological and neurological effects Pregnancy/Neonate Data: Testicular atrophy, teratogenicity, fetotoxicity Genotoxicity Data: Limited evidence is negative Carcinogenicity Classification: IARC - No data NTP - Study in progress EPA - No data
HANDLING PRECAUTIONS (54)	Handle chemical only with adequate ventilation • Vapor concentration of 250 ppm or less: any supplied-air respirator or self-contained breathing apparatus • Vapor concentrations of 250-1250 ppm: any supplied-air respirator or self contained breathing apparatus with full facepiece • Vapor concentrations of 1250-2000 ppm: type C supplied-air respirator with full facepiece operated in pressure-demand mode. Wear appropriate protective clothing and chemical goggles if any possibility of eye contact.

ENVIRONMENTAL AND OCCUPATIONAL STANDARDS AND CRITERIA

AIR EXPOSURE LIMITS:

Standards
- OSHA TWA (8-hr): 25 ppm (skin)
- AFOSH PEL (8-hr TWA): 25 ppm (skin); STEL (15-min): 37.5 ppm

Criteria
- NIOSH IDLH (30-min): Not applicable because of NIOSH REL.
- NIOSH REL.: The lowest feasible limit
- ACGIH TLV® (8-hr TWA): 5 ppm (skin)
- ACGIH STEL (15-min): None established

WATER EXPOSURE LIMITS:

Drinking Water Standards
None established

EPA Health Advisories and Cancer Risk Level
None established

WHO Drinking Water Guideline
No information available.

EPA Ambient Water Quality Criteria
- Human Health (355)
  - No criterion established. Methyl Cellosolve® is not a priority pollutant.
- Aquatic Life (355)
  - No criterion established. Methyl Cellosolve® is not a priority pollutant.

REFERENCE DOSES:
No reference dose available.

REGULATORY STATUS (as of 01-MAR-89)

Promulgated Regulations

- Federal Programs

  Comprehensive Environmental Response, Compensation and Liability Act (CERCLA)
  Under SARA Title III Section 313, manufacturers, processors, importers, and users of Methyl Cellosolve® must report annually to state and EPA officials their releases of this chemical to the environment (3787).

  Federal Insecticide, Fungicide and Rodenticide Act (FIFRA)
  Methyl Cellosolve® is exempt from a tolerance requirement when used as a solvent for formulations used before crops emerge from the soil (315).

  Marine Protection Research and Sanctuaries Act (MPRSA)
  Ocean dumping of organohalogen compounds as well as the dumping of known or suspected carcinogens, mutagens or teratogens is prohibited except when they are present as trace contaminants. Permit applicants are exempt from these regulations if they can demonstrate that such chemical constituents are non-toxic and non-bioaccumulative in the marine environment or are rapidly rendered harmless by physical, chemical or biological processes in the sea (309).

  Occupational Safety and Health Act (OSHA)
  Employee exposure to Methyl Cellosolve® shall not exceed an 8-hour time-weighted average (TWA) of 25 ppm. This is a Transitional Limit, in effect until EPA promulgates the new standards it is currently working on (3539).

  Food, Drug and Cosmetic Act (FDCA)
  Methyl Cellosolve® is approved for use as an indirect food additive as a component of adhesives (3209).

- State Water Programs

  ALL STATES
  Although all states have adopted EPA Ambient Water Quality Criteria and NPDWRs as their promulgated state regulations, either by narrative reference or by relisting specific numeric criteria, numeric criteria have not been established under the CWA or NPDWRs for Methyl Cellosolve®. There are also no state regulations specific to this chemical.

Proposed Regulations

- Federal Programs

Occupational Safety and Health Act (OSHA)
OSHA has determined that the existing PEL for Methyl Cellosolve® is inadequate to protect workers from significant health risks and will propose a revised standard (1235).

- State Water Programs

NONE
No proposed regulations are pending.
MOST STATES
Most states are in the process of revising their water programs and proposing changes to their regulations which will follow EPA's regulations when they become final. Contact with the state officers is advised. Changes are projected for 1989-90 (3683).

EEC Directives

Directive on Ground-Water (538)
Direct discharge into ground-water (i.e., without percolation through the ground or subsoil) of organophosphorous compounds, organohalogen compounds and substances which may form such compounds in the aquatic environment, substances which possess carcinogenic, mutagenic or teratogenic properties in or via the aquatic environment and mineral oils and hydrocarbons is prohibited. Appropriate measures deemed necessary to prevent indirect discharge into ground-water (i.e., via percolation through ground or subsoil) of these substances shall be taken by member countries.

Directive Relating to the Classification, Packaging and Labeling of Dangerous Preparations (Solvents) (544)
Methyl Cellosolve® is listed as a Class II/c harmful substance and is subject to packaging and labeling regulations.

Directive on Marketing and Use of Dangerous Substances (541)
Methyl Cellosolve® may not be used in ornamental objects intended to produce light or color effects by means of different phases.

Directive on Toxic and Dangerous Wastes (542)
Any installation, establishment, or undertaking which produces, holds and/or disposes of certain toxic and dangerous wastes including phenols and phenol compounds; organic-halogen compounds; chrome compounds; lead compounds; cyanides; ethers and aromatic polycyclic compounds (with carcinogenic effects) shall keep a record of the quantity, nature, physical and chemical characteristics and origin of such waste, and of the methods and sites used for disposing of such waste.

Directive on the Classification, Packaging and Labeling of Dangerous Substances (787)
Methyl Cellosolve® is classified as a harmful substance and is subject to packaging and labeling regulations.

EEC Directives - Proposed
Resolution on a Revised List of Second-Category Pollutants (545)
Methyl Cellosolve® is one of the second-category pollutants to be studied by the Commission in the programme of action of the European Communities on Environment in order to reduce pollution and nuisances in the air and water. Risk to human health and the environment, limits of pollutant levels in the environment, and determination of quality standards to be applied will be assessed.

42.1 MAJOR USES

Methyl Cellosolve® is an industrial solvent used primarily in the aviation industry. Approximately 47% of the Methyl Cellosolve® produced is used as a jet fuel anti-icing additive. The remainder is used for resins, lacquers, paints, varnishes, gum, perfume, dyes and inks and as a constituent of cleaning compounds, liquid soaps, cosmetics and hydraulic fluids (2, 54, 59).

42.2 ENVIRONMENTAL FATE AND EXPOSURE PATHWAYS

42.2.1 Transport in Soil/Ground-water Systems

42.2.1.1 Overview

Methyl Cellosolve® is expected to be highly mobile in the soil/ground-water system when present at relatively low concentrations or as a separate organic phase (resulting from a spill of significant quantities of the chemical). In general, transport pathways can be assessed by using an equilibrium partitioning model, as shown in Table 42-1. These calculations predict the partitioning of low soil concentrations of Methyl Cellosolve® among soil particles, soil water and soil air. Portions of Methyl Cellosolve® associated with the water and air phases of the soil have higher mobility than the sorbed portion.

Estimates for the unsaturated topsoil model indicate that 1.5% of the Methyl Cellosolve® is expected to be sorbed onto soil particles. Approximately 98.5% is expected to partition to the mobile soil-water phase, and is thus available to migrate by bulk transport (e.g., the downward movement of infiltrating water), dispersion and diffusion. Since an insignificant portion of the Methyl Cellosolve® is expected to be in the gaseous phase of the soil (0.0001%), diffusion through the soil-air pores up to the ground surface and subsequent removal by wind would appear to be a minor loss pathway. In saturated, deep soils (containing no soil air and negligible soil organic carbon), almost all of the Methyl Cellosolve® (99.97%) is predicted to be present in the soil-water phase (Table 42-1) and available for transport with flowing ground-water. Sorption onto deep soils (0.03%) is not expected to be significant. Overall, ground-water underlying Methyl Cellosolve® contaminated soils with low organic content is expected to be vulnerable to contamination.

42.2.1.2 Sorption on Soils

The mobility of Methyl Cellosolve® in the soil/ground-water system (and its eventual migration into aquifers) is controlled by the extent of its sorption onto soil

TABLE 42-1
EQUILIBRIUM PARTITIONING CALCULATIONS FOR METHYL CELLOSOLVE® IN MODEL ENVIRONMENTS[a]

Soil Environment	Estimated Percent of Total Mass of Chemical in Each Compartment		
	Soil	Soil-Water	Soil-Air
Unsaturated topsoil at 25°C[b,c]	1.5	98.5	1E-04
Saturated deep soil[d]	0.03	99.97	-

a) Calculations based on Mackay's equilibrium partitioning model (34, 35, 36); see Introduction in Volume 1 for description of model and environmental conditions chosen to represent an unsaturated topsoil and saturated deep soil. Calculated percentages should be considered as rough estimates and used only for general guidance.
b) Utilized soil sorption estimated with equations of Means et al. (611): K_{oc} = 0.08.
c) Henry's law constant taken as 8E-09 atm · m³/mol at 25°C estimated according to method of Hine and Mookerjee (966).
d) Sorption coefficient calculated as a function of K_{oc} assuming 0.1% organic carbon: $K_p = 0.001 \times K_{oc}$).

particles. Methyl Cellosolve® is miscible in water and, as evidenced by its negative log K_{ow} and low K_{oc}, adsorption to soil/sediments is not expected to significantly influence its environmental fate.

No data specific to sorption of Methyl Cellosolve® on soils were available. However, behavior of Methyl Cellosolve® is expected to be similar to that of ethylene glycol or acetone, both migrating freely through the soil/ground-water system with little or no retardation (862, 1122).

42.2.1.3 Volatilization from Soils

Transport of Methyl Cellosolve® vapors through the air-filled pores of unsaturated soils may occur in near surface soils. However, modeling results suggest that only a small fraction of the Methyl Cellosolve® loading will be present in the soil-air phase.

In general, important soil and environmental properties influencing the rate of volatilization include soil porosity, temperature, convection currents and barometric pressure changes; important physico-chemical properties include the Henry's law constant, the vapor-soil sorption coefficient, and, to the lesser extent, the vapor phase diffusion coefficient (31).

Data on Methyl Cellosolve® volatilization from soils, in particular, are not available. Methyl Cellosolve® is not strongly sorbed to soil and is highly soluble in water. Although some volatilization may occur at the surface, the low value estimated for the Henry's law constant (3E-09 atm · m^3/mole) suggests that vapor concentrations will be low whenever water is present and volatilization will be minimal.

42.2.2 Transformation Processes in Soil/Ground-water Systems

No information was available on the nonbiological degradation of Methyl Cellosolve® under environmental conditions.

The data on microbial degradation of Methyl Cellosolve® in pure cultures are limited and inconclusive (859, 861). Degradation using activated sludge and acclimated sewage seed has been reported to be fairly significant with BOD5 values ranging from 7% to 65% (880, 860, 881, 882).

Based on the limited data available, prediction of biodegradation rates in the environment is not possible. Furthermore, in most soil/ground-water systems, the concentrations of microorganisms capable of biodegrading Methyl Cellosolve® may be low, and drop off sharply with depth. Thus, biodegradation may be of minimal importance except, perhaps, near landfills with active microbiological populations.

42.2.3 Primary Routes of Exposure from Soil/Ground-water Systems

The above discussion of fate pathways suggests that Methyl Cellosolve® is effectively nonvolatile, is very weakly sorbed to soil, and has little potential for bioaccumulation. These fate characteristics suggest several potential exposure pathways.

The potential for ground-water contamination with Methyl Cellosolve® is high, particularly in sandy soils. It has not been reported in ground water associated with hazardous waste sites, but the properties of Methyl Cellosolve® suggest that drinking water exposure from ground-water contamination is likely to be its primary route of exposure from soil/ground-water systems.

The movement of Methyl Cellosolve® in ground water may result in discharge to surface water. As a result, ingestion exposures may occur resulting from the use of surface waters as drinking water supplies, and dermal exposures may result from the recreational use of surface waters. Such exposures are likely to be lower than those

from drinking contaminated ground water due to degradation of Methyl Cellosolve® in surface water. Any pathways related to the uptake by aquatic organisms or domestic animals from surface waters are likely to be less significant than other sources of exposure due to the low BCF for Methyl Cellosolve®.

42.2.4 Other Sources of Human Exposure

Methyl Cellosolve® is used as a solvent in a variety of products and as a constituent of printing pastes, cleaning compounds, liquid soaps and cosmetics. As such, there are likely to be a number of sources of human exposure.

Dermal exposure, in particular, is possible in some situations due to the use of Methyl Cellosolve® in these products. For example, two surveys were conducted in Japan on the solvent content of a variety of products. They found Methyl Cellosolve® in 4% of the inks, 1% of the adhesives and 3% of the thinners that were sampled. While most of these products were used in occupational settings, some may be used by consumers (1140, 1141).

42.3 HUMAN HEALTH CONSIDERATIONS

42.3.1 Animal Studies

42.3.1.1 Carcinogenicity

No data were found.

42.3.1.2 Genotoxicity

Methyl Cellosolve® did not produce histidine revertants when tested in strains TA1535, TA1537, TA98 and TA100 of Salmonella typhimurium, both with and without metabolic activation (1060), and in the five standard strains (those above and TA1538) tested at dose levels of up to 33 mg per plate with 30 minutes preincubation (3438). It also failed to induce forward mutations at the adenine locus in the yeast Schizosaccharomyces pombe (3001). It did, however, block junction-mediated intercellular communication in Chinese hamster V79 cells (1061).

McGregor et al. (3438) also observed negative results in a battery of tests on this compound: unscheduled DNA synthesis in human embryo fibroblasts (3 hrs exposure in up to 10 mg/mL); chromosome aberrations in bone marrow cells of male and female rats treated with 25 ppm, 7 hrs, for one or five days; and the Drosophila melanogaster sex-linked recessive lethal assay.

Foster et al. (3224) observed extreme toxicity in meiotic cells of male Sprague-Dawley rats given 500 mg/kg Methyl Cellosolve® orally for 4 days but the majority of

the tubules recovered their spermatogenic potential within one full maturation cycle after treatment was stopped.

Most of the rodent dominant lethal studies that have been published indicate negative or inconclusive results complicated by the toxicity this compound displays in male meiotic cells. McGregor et al. (3438) treated male CD rats with 500 ppm Methyl Cellosolve® 7 hrs/day for 5 days with inconclusive results. Pregnancy frequencies and total implantations per female were not significantly different from those of controls at weeks 1 and 2, but were greatly reduced at weeks 3 and 4 and totally absent at week 5. Due to a profound decrease in male fertility, it was not possible to detect an increase in early fetal deaths indicative of a true dominant lethal effect. Exposure at a level of 25 ppm produced no reduction in the above parameters. Anderson et al. (3025) also observed no statistically significant evidence for the induction of dominant lethals in male mice or rats treated with 0, 500, 750, 1000, or 1500 mg/kg given as a single oral dose even though sperm counts were severely depressed in both species and morphologically abnormal sperm were the rule in treated rats. Chapin et al. (3110) treated male F344 rats orally with 50, 100 or 200 mg/kg/day for 5 days and concluded that Methyl Cellosolve® is a "very weak inducer" of dominant lethal mutations. Rao et al. (3581) treated Sprague-Dawley males with 30 or 100 ppm Methyl Cellosolve® 6 hrs/day, 5 days a week, for 13 weeks and observed no dominant lethal effects. Males receiving 300 ppm with the same regimen were completely sterile, and their fertility was partially restored 13 weeks after cessation of treatment.

42.3.1.3 Teratogenicity, Embryotoxicity and Reproductive Effects

Methyl Cellosolve® causes both teratogenic and adverse male reproductive effects in several species. The effect of Methyl Cellosolve® vapor on pregnant rats was evaluated by Nelson et al. (1059). Sprague-Dawley rats were exposed to 0, 50, 100, or 200 ppm of Methyl Cellosolve® vapor for 7 hours/day on days 7-15 of gestation. No signs of maternal toxicity were observed. Fetuses were examined on day 20. Methyl Cellosolve® was highly embryotoxic at all treatment levels with an increase in resorption and reduced fetal weight occurring at both the 50 and 100 ppm level. Complete fetal resorption occurred at the 200 ppm level. Heart abnormalities were the predominant malformation observed in both the 50 and 100 ppm groups. Other terata occurring at a lower frequency affected the retina, the eyes, the umbilicus and the lungs. Skeletal aberrations at both the 50 and 100 ppm levels included wavy, fused and absent ribs, and extra vertebrae. Tail malformations were also observed in the 100 ppm group (1059).

Groups of 24-32 pregnant Fischer 344 rats, CF-1 mice and New Zealand white rabbits were exposed to 0, 50, 200, or 400 ppm Methyl Cellosolve® vapor for 6 hours/day on days 6-15 (rats and mice) or on days 6-18 (rabbits) of gestation. Complete embryolethality resulted at the 200 and 400 ppm levels. Mice were then exposed to 0, 10, or 50 ppm Methyl Cellosolve® vapor, while rats and rabbits were exposed to 0, 3, 10, or 50 ppm Methyl Cellosolve® vapor during the period of major

organogenesis. Methyl Cellosolve® was not teratogenic in Fischer 344 rats exposed to concentrations of up to 50 ppm for 6 hours/day, although a slight fetotoxic effect was observed at the 50 ppm level as shown by a statistically significant increase in the incidence of lumbar spurs (57 vs. 18 in the control group) and a delayed vertebrae centra ossification (19 vs. 4 in the control group). No teratogenic response was observed in the CF-1 mice at any treatment level; however, there was an indication of fetotoxicity at the 50 ppm level. Rabbits exposed to 50 ppm experienced a significant increase in the resorption rate (24 vs. 4 in the control groups). Also, mean fetal body weight in this group was significantly reduced (35.88 vs. 39.57 in the control groups). At this level, all organ systems in the rabbit were involved in a significant incidence of malformations. Forty-three percent of the fetuses had ventricular septal defects, 16% of which exhibited a constriction of the aortic arch. Severe splenic hypoplasia was evident, and in several cases the spleen was nearly invisible. No effects were reported in fetuses of rabbits exposed to the 3 or 10 ppm levels (1062).

Nagano et al. (1063) investigated the effects of Methyl Cellosolve® ingestion upon fetal development in mice. Pregnant JCL-ICR mice were given 31.25, 62.5, 125, 250, 500, or 1000 mg of Methyl Cellosolve/kg of body weight/day by gastric intubation on days 7-14 of gestation. A decrease in maternal body weight gain was observed in the 250, 500, and 1000 mg/kg groups. The 1000 mg/kg group also exhibited a significant decrease in the white blood cell count. All fetuses in the 1000 mg/kg group were dead and only one fetus survived in the 500 mg/kg group. This fetus had exencephaly and abnormal digits. There was a significant reduction in fetal weight at both the 125 and 250 mg/kg doses. Exencephaly, abnormal digits and umbilical hernias were the major gross abnormalities observed in the 250 mg/kg group. The incidence of oligodactyly (less than usual number of digits) was statistically significant in the 250 mg/kg group (17 cases). Syndactyly (webbing between adjacent digits) was observed in 9 fetuses in the 250 mg/kg group, but was not considered to be statistically significant. All examined fetuses of the 250 mg/kg group had skeletal malformations including fused and/or poorly developed ribs and vertebrae, and spina bifida occulta. In the 125 mg/kg group, 51.12% of the fetuses exhibited these same types of malformations. Similar but not statistically significant malformations were also observed in the 31.25 and 62.5 mg/kg groups. All skeletal effects followed a dose-dependent trend. Nagano et al. concluded that Methyl Cellosolve® was capable of producing teratogenic effects in mice although only mild maternal toxicity was observed.

The Chemical Industry Institute of Toxicology has conducted several studies on the effect of Methyl Cellosolve® in CD-1 mice (3299, 3662, 3255, 3833). Pregnant mice received multiple or single doses by gavage between gestational days 7 and 14. No maternal toxicity was observed after multiple doses of 250 mg/kg or single doses of up to 500 mg/kg. The observed fetal malformations on gestation day 18 were specifically related to the developmental stage at the time of exposure. When exposures occurred between days 7 and 10 exencephaly resulted. Paw anomalies (syndactyly, oligodactyly and stunted digit no. 1) were maximal after exposure on

gestation day 11. The No Observed Effect dose for induction of digit malformations on day 11 was 100 mg/kg in a single oral dose. At 175 mg/kg digit anomalies were induced but no reduction in fetal body weight was observed. The 250 mg/kg and above doses resulted in digit anomalies and reduced fetal body weight.

Hardin and Eisenmann (3269) investigated paw malformations in CD-1 mice with exposure by gavage of pregnant females to 304 mg/kg of Methyl Cellosolve® on gestational day 11. This dose level resulted in no effect on maternal body weight at term. No decrease in live litter size or fetal body weight compared to control values was observed on gestational day 18. Paw defects were present in 87.5% of the litters (68.5% of the fetuses). Hindpaw defects predominated over forepaw, and syndactyly was the most frequent malformation.

The male reproductive system is also adversely affected by Methyl Cellosolve®. Rao et al. (1056) exposed groups of male and female Sprague- Dawley rats to 0, 30, 100, or 300 ppm Methyl Cellosolve® vapor for 6 hours/day, 5 days/week for 13 consecutive weeks. At the end of the exposure period, rats were allowed to breed with unexposed rats. The mean body weights of male rats treated with 300 ppm of Methyl Cellosolve® were significantly decreased throughout the study. Female rats exposed to 300 ppm of Methyl Cellosolve® also showed a statistically significant decrease in body weight beginning on the 7th week of exposure. No decrease in fertility was observed among any of the treated females. Male fertility was based on the ability to impregnate unexposed females. There was no apparent effect on mating behavior; however, the fertility indices of the male rat exposed to 300 ppm were significantly decreased (20% vs. 97%). Only 4 of 20 females were impregnated and all 4 impregnations resulted in complete resorption. These males were bred again at 13 and 19 weeks post-exposure. Fertility was still decreased during these breeding periods; however, 50% of the males previously exposed to 300 ppm Methyl Cellosolve® sired litters in which the majority of implantations appeared viable (1056).

In order to determine the nature of the infertility observed in males, male F344 rats were given 150 mg/kg/day Methyl Cellosolve® in distilled water perorally 5 days/week. Animals were sacrificed 1, 2, 4, 7 and 10 days after the first dose and testicular tissue was examined. By the fourth day, the spermatid population decreased in affected tubules as the precursor spermatocytes died. Effects appeared to be specific for the spermatocyte stage of development and resulted in a depletion of the spermatid population which was not being replenished. Several indices of sertoli cell function were examined and found to be unaffected by Methyl Cellosolve®. Chapin et al. (1057) concluded that the spermatocytes were the first cells to undergo necrotic changes after treatment of F344 rats with Methyl Cellosolve®.

Foster et al. (1058) administered 50, 100, 250, or 500 mg/kg/day of Methyl Cellosolve® by gavage to rats. Six animals from each treatment group were killed 6 and 24 hours after the first dose. Other animals from each treatment group were killed on days 2, 4, 7 and 11. Another group of animals were given 500 mg/kg/day of

Methyl Cellosolve® for 4 days. Rats were then killed at 0, 2, 4 and 8 weeks post-ingestion. A decrease in testicular weight was observed in the 500 mg/kg/day treatment group on day 2 of testing, which became more pronounced as time progressed. By day 7, testes weights for both the 250 mg and the 500 mg groups were significantly less than the control weights. Histological examination again revealed degeneration of the spermatocytes, but in this case, damage was evident 24 hours after a single treatment of 100, 250, or 500 mg/kg/day and necrosis progressed in a dose-related fashion. By day 11, treatment with 250 or 500 mg/kg/day had resulted in a cessation of the sperm maturation process. Testicular weight did not begin to recover until 2 weeks after the last treatment and testes weights did not reach control levels until 8 weeks after the last treatment was given (1058).

Adult male CD rats and CD-1 mice were given a single oral dose of Methyl Cellosolve® at 500, 750, 1000, or 1500 mg/kg in a study conducted by Anderson et al. (3025). The agent was found to deplete the spermatocytes of both species severely. In the rat morphological abnormalities were observed in sperm that had been exposed as spermatocytes; in the mouse, however, the sensitive cells were the late spermatocytes and early spermatids. In mating studies in the rat, a dose-related decrease in fertility was found 5 weeks after dosing, but complete sterility resulted in all but the lowest dose after 6 weeks. Methyl Cellosolve® had no effect on the reproductive capacity of the male mouse. No statistically significant evidence was observed for dominant lethal mutations or F_1 abnormalities in either species.

A recent study by Scott et al. (3630) reported that a metabolite of Methyl Cellosolve®, methoxyacetic acid, was found in the extra-embryonic fluid in pregnant rats 2, 8, or 24 hours after ip injection of 400 mg/kg of Methyl Cellosolve® on day 12 of gestation. When fetuses were removed on day twenty, 86 out of 87 fetuses had fore- or hindlimb malformations. Ten of these fetuses had digital duplications. Morphological observation indicated that the limb bud periderm was severely damaged by the agent so that large patches of the structure were actually missing during an extended period of limb bud development. A high concentration of methoxyacetic acid found in the extra-embryonic fluid caused the investigators to postulate that the damage to the periderm was initiated from this exposure.

42.3.1.4 Other Toxicologic Effects

42.3.1.4.1 Short-term Toxicity

In addition to the adverse reproductive effects of Methyl Cellosolve®, the blood and nervous system are prime targets of toxicity. Anemia, abnormal leukocytes, kidney damage and metabolic acidosis are signs associated with Methyl Cellosolve® poisoning. The oral LD_{50} is listed as 2460 mg/kg for rats (51). The LC_{50} for mice inhaling Methyl Cellosolve® for 7 hours is 1500 ppm (51).

Heinonen and Vainio (1065) studied the dose-dependent toxicity of Methyl Cellosolve® vapor on the liver and kidney of the rat. Male Wistar rats were exposed

to 50, 100 or 400 ppm of Methyl Cellosolve® for 6 hours/day, 5 day/week for 1 or 2 weeks. NADPH cytochrome c reductase activity showed a significant dose-related decrease in the liver, while UDP-glucuronosyl transferase activity showed a significant dose-related increase. Glutathione levels showed a dose-related increase in the liver and kidneys. Oxalate crystals were present in the renal tubules. Heinonen and Vainio speculated that the calcium oxalate and the resultant metabolic acidosis was possibly the result of the decomposition of Methyl Cellosolve® to methanol and ethylene glycol.

Male and female Fischer 344 rats and B6C3F$_1$ mice were exposed to 0, 100, 300 or, 1000 ppm Methyl Cellosolve® vapor for 6 hours/day on 5 consecutive days followed by 4 additional consecutive exposures after a 2-day interruption (9 exposures in an 11-day interval) (1065). Growth of both the male and female rats in the 1000 ppm Methyl Cellosolve® group was significantly retarded. The mean body weight gains of female rats in the 100 and 300 ppm groups were significantly lower than the controls. The packed cell volume, red and white blood cell counts and hemoglobin of both male and female rats in the 1000 ppm Methyl Cellosolve® group were significantly decreased over the controls. Significant, but less severe, alterations of the hematological parameters were observed in the groups of rats and mice exposed to 300 ppm Methyl Cellosolve®. Rats exposed to 1000 ppm Methyl Cellosolve® exhibited severe degeneration of the germinal epithelium in the testes, severe lymphoid depletion in the cortex of the thymus and a reduced number of lymphoid cells in the spleen and mesenteric lymph nodes. Effects were similar but less severe in the 300 ppm groups, while no treatment-related changes were observed in the 100 ppm groups. A markedly reduced bone marrow cellularity, shown by a drastically reduced number of myeloid and erythroid cells and a slight increase in immature cells was also observed. The tissues primarily affected by Methyl Cellosolve® all have a relatively high rate of cell division which suggests that Methyl Cellosolve® may produce its toxic effects by inhibiting mitotic processes. However, since all tissues with a high rate of cellular division are not affected, Methyl Cellosolve® target organ specificity must involve other factors.

Romer et al. (1070) found that administration of Methyl Cellosolve® in combination with ethanol to rats produced an accumulation of ethylene glycol monomethyl ether in the blood stream. Both ethylene glycol monomethyl ether and ethanol are believed to compete for the metabolizing enzyme, alcohol dehydrogenase (ADH). The affinity of ADH for ethanol is greater than its affinity for ethylene glycol monomethyl ether. This results in a metabolism of the ethanol but an inhibition of the degradation of ethylene glycol monomethyl ether.

42.3.1.4.2 Chronic Toxicity

Miller et al. (1067) exposed Sprague-Dawley rats and New Zealand white rabbits to 0, 30, 100 or 300 ppm Methyl Cellosolve® vapor 6 hours/day, 5 days/week for 13 weeks. Mean body weights of both rats and rabbits exposed to 300 ppm were significantly lower than the control animals. In rats, gross lesions attributed to Methyl Cellosolve® exposure occurred at the 300 ppm level only. There was a decrease in thymus size and weight, small flaccid testes in the males and a decrease in abdominal adipose tissue in some of the females. In rabbits, the males appeared to be affected at all 3 exposure levels while female rabbits were affected at only the 100 and 300 ppm levels. Effects were similar to those observed in the rat; however, they were more severe and followed a dose-dependent pattern. Signs included a reduction of body weight, hematologic changes, lymphoid tissue atrophy and degeneration of testicular germinal epithelium. Miller believed that despite the lack of bone marrow response in this study, the primary effect of Methyl Cellosolve® is on hematopoiesis (1067).

Grant et al. (3250) administered Methyl Cellosolve® to male F344 rats per os for 4 days at doses of 100 or 500 mg/kg/day. Animals were killed on days 1, 4, 8 and 22. The major hematological effect was leukopenia associated with reductions in lymphocytes and neutrophils. Bone marrow toxicity was evident in the form of severe hemorrhage of the endothelial cells lining the sinuses. Reductions in thymic weights were observed, with a loss of lymphocytes from the thymic cortex.

Male Hartley guinea pigs dermally exposed to 1 g/kg/day Methyl Cellosolve® 6 hours/day, 5 days/week for 13 weeks developed body weight loss and reduced testicle and spleen weights. Hematologic alterations include mild anemia and a lymphopenia with increased neutrophils. These data indicate Methyl Cellosolve® readily penetrates the skin and produces toxic effects similar to other routes of exposure (1789).

42.3.2 Human and Epidemiologic Studies

42.3.2.1 Short-term Toxicologic Effects

Human exposure to Methyl Cellosolve® generally results in hematologic and CNS disorders. Symptoms tend to mimic those of ethylene glycol intoxication.

Nitter-Hauge (1068) reported two cases of Methyl Cellosolve® poisoning. Two men inadvertently drank approximately 100 mL of Methyl Cellosolve®. Several hours later, after a symptom-free interval of 8-18 hours, they appeared ill and were taken to a hospital. Symptoms included cerebral confusion, deep and frequent respiration and a profound metabolic acidosis. One man exhibited renal failure with persistent oxaluria. Both men recovered and were discharged 3-4 weeks after admission.

Young and Woolner (1069) reported another case of Methyl Cellosolve® ingestion. The man was believed to have consumed 200 mL of Methyl Cellosolve® mixed with liquor. He was admitted to the hospital in a comatose condition and died 5 hours later. Autopsy revealed hemorrhagic gastritis, marked degeneration of the kidney tubules and fatty degeneration of the liver. The fatal outcome of this case may be linked to the patient's simultaneous ingestion of ethanol with Methyl Cellosolve®.

42.3.2.2 Chronic Toxicologic Effects

Chronic Methyl Cellosolve® toxicity is a condition which is very difficult to diagnose unless definite knowledge of exposure is known to have occurred. Symptoms of chronic exposure to Methyl Cellosolve® usually include headache, dizziness, lethargy, weakness, unequal pupil size, disorientation, the appearance of mental retardation and personality changes. Ataxia, anemia and disturbances in vision and hearing have been reported. The overall chronic condition has on occasion been mistakenly diagnosed as schizophrenia (17).

Zavon (1072) described a case involving the admission of a young man to a hospital in a nervous and tense state. Prior to hospitalization he complained of weakness, a need for more sleep than usual, loss of appetite, dazed preoccupied look and the reoccurrence of a stutter. Physical examination was normal. The individual was diagnosed as suffering from a confused state and was treated for schizophrenia with a series of electroshock treatments. He was released from the hospital 2 weeks later. He still complained of nervousness but the stuttering had disappeared. It was later discovered that this man worked in the printing department of a plastics plant where Methyl Cellosolve® was frequently used to clean the presses. A diagnosis of Methyl Cellosolve® intoxication was made retrospectively. Estimated atmospheric concentrations of Methyl Cellosolve® to which this worker was exposed ranged from 61-3960 ppm.

Ohi and Wegman (1073) investigated 2 reports of encephalopathy resulting from dermal exposure to Methyl Cellosolve®. Both individuals were employed in an electroplating facility where jets of acetone spray were used on the equipment and cleaned by rubbing the metal with bare hands. For about 6 months, from spring to fall, Methyl Cellosolve® was substituted for acetone. Air samples showed an average Methyl Cellosolve® concentration of 8 ppm, well below the 25 ppm TLV ®. The first affected employee was hospitalized in August in a confused state. During examination he was disoriented and lapsed in and out of sleep. During the preceding 2-3 months he suffered from lethargy, unusual sleepiness, decreased hearing, anorexia and weight loss. The white cell count was 2600 (4300-10,800 is the normal range) and bone marrow aspiration revealed marrow depression with some signs of recovery. The worker was treated for encephalopathy and his condition improved over several weeks. The second case was admitted in September with a cough, shortness of breath, fever, lethargy, staggering gait, blurred vision, slurred speech, poor memory, headache, confusion, anorexia, nausea, vomiting and bed wetting. The blood test

appeared normal; however, a bone marrow aspiration revealed severe marrow damage. The worker was not treated, but remained in the hospital for observation. All symptoms disappeared within one week. These 2 cases of Methyl Cellosolve® poisoning occurred via a strictly cutaneous route, and in an environment in which air concentrations were considerably below the threshold limit of 25 ppm (1073).

Nakaaki et al. (1075) investigated the ability of Methyl Cellosolve® to penetrate human skin. High blood levels of ethylene glycol monomethyl ether were found following dermal exposure to 15 mL of undiluted Methyl Cellosolve® for 2 hours. The information provided by Ohi (1073) and Nakaaki (1075) also indicates that dermal absorption is a significant route of exposure for Methyl Cellosolve®.

Another report of Methyl Cellosolve® intoxication involves a coating and mixing operator in a microfilm lab. After approximately 6 months of exposure, this operator complained of an increase in sleep time a 20-pound increase in body weight despite a decreased appetite, and an increased feeling of reserve. White and red cell counts, hemoglobin, hematocrit and platelets had all dropped to abnormally low levels. The worker continued at his job, which involved regular inhalation and dermal exposure to 18.2-57.8 ppm of Methyl Cellosolve®, for another year. During this year, physical examinations were normal, but macrocytic anemia persisted. At one year, he was removed from all Methyl Cellosolve® exposure. Within one month, hematologic parameters had returned to normal (1074). Again, this hematologic picture typifies chronic Methyl Cellosolve® toxicity. The absence of CNS toxicity suggests that exposure levels were very low.

Recent toxicological studies have reported testicular atrophy and sterility in animals exposed to Methyl Cellosolve® (1056, 1057, 1058). A cross-sectional study was conducted by Cook et al. (1071) to determine if employees exposed to Methyl Cellosolve® had an increased prevalence of anemia, leukopenia or sterility over those not exposed. Only 6 potentially exposed and 9 control employees were used in the fertility portion of the study. The results indicated that no gross abnormalities or clinically meaningful differences in fertility existed among the potentially exposed and control employees other than a potentially decreased testicular size among the potentially exposed employees.

42.3.3 Levels of Concern

The current OSHA (3539) standard is 25 ppm (skin) averaged over an 8-hour workshift; revision of this standard, however, is under consideration (3539) based on recent animal studies which suggest that the presently recommended exposure limit may not afford an adequate safety margin. The ACGIH (291) recommends a 5 ppm TWA, with a notation of possible skin absorption.

42.3.4 Hazard Assessment

Methyl Cellosolve® is moderately toxic by ingestion and inhalation and is readily absorbed through the skin. In humans, symptoms of intoxication with this compound include nausea, headache, vomiting, hematological disorders and kidney damage.

Animal data are remarkable in their consistency of effects across species lines within defined exposure ranges. Methyl Cellosolve® has been shown to induce hematological effects characterized by reduction in red and white blood cell counts, bone marrow depression, testicular atrophy, fetotoxicity and teratogenicity. These effects are observed following all routes of exposure.

Hematological effects have been documented in mice, rats, rabbits, guinea pigs and humans (1066, 1067, 1789, 17, 1074) within an exposure range of 100 to 1000 ppm. Degenerative changes in the testis have also been identified in a range of animal species (1058, 1056) and fetotoxic and teratogenic effects have been noted in rats, mice and rabbits (1059, 1062, 1063) at exposure levels in the range of 50 ppm. In mice and rats the most frequently observed teratogenic effects were paw malformations (3269, 3630). These malformations included syndactyly, oligodactyly and stunted digit no. 1, and were maximal following exposure on gestational day 11 in mice (3299, 3662, 3255, 3833).

Effects on the testes and developing embryo do not appear to be associated with interactions with DNA, even though spermatogenesis is severely affected but not irreversibly. Methyl Cellosolve® does not appear to pose a genotoxic hazard. It did not induce mutations in either bacteria, yeast, or mammalian cell culture systems (1016, 1284, 3001, 3438) and provided negative indications of a dominant lethal effect in rats and mice (3438, 3581, 3025, 3110). There are no data available regarding the carcinogenicity of Methyl Cellosolve®.

The similarity of toxic effects resulting from exposure to Methyl Cellosolve® in several species and evidence of hematological effects in humans at exposure levels which induce hematological effects in animals suggest it is prudent to assume that effects on testes and the developing embryo seen in animals at lower exposure levels may also occur in similarly exposed humans.

42.4 SAMPLING AND ANALYSIS CONSIDERATIONS

Determination of the concentration of Methyl Cellosolve® in soil and water requires collection of a representative field sample and laboratory analysis. Due to the volatility of Methyl Cellosolve®, care is required to prevent losses during sample collection and storage. Soil and water samples should be collected in airtight containers with no headspace; analysis should be completed within 14 days of samples. In addition to the targeted samples, quality assurance samples such as field blanks, duplicates, and spiked matrices should be included in the analytical program.

Methyl Cellosolve® is not included among the EPA-designated priority pollutants, and an EPA-approved procedure for the analysis of Methyl Cellosolve® is not available. However, the recommended analytical methods for alcohols and ethers (1142) is gas chromatography with flame ionization detection (GC/FID). Samples may either be directly injected onto the gas chromatographic (GC) column (aqueous and organic liquid samples) or may first be extracted with methylene chloride or toluene and the concentrated extract injected onto the GC column (aqueous and solid samples). Detection of Methyl Cellosolve® is then accomplished by a flame ionization detector. A mass spectrometer using either electron impact (EI) or chemical ionization (CI) techniques may also be used to detect Methyl Cellosolve®.

A detection limit for Methyl Cellosolve® using these methods was not determined but would be in the range of ug/L for aqueous samples and ug/g for non-aqueous samples which have been extracted and in the range of ppm for samples which have been directly injected.

42.5 REFERENCES

Note: The nonsequential numbers of the references reflect the order of references as they appear in the master bibliography.

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ETHYLENE GLYCOL

COMMON SYNONYMS:	CAS REG.NO.: 107-21-1 FORMULA: $C_2H_6O_2$ NIOSH NO: KW2975000 STRUCTURE: $HO\text{-}CH_2CH_2OH$	AIR W/V CONVERSION FACTOR at 25°C (12) 2.54 mg/m³ ≈ 1 ppm; 0.365 ppm ≈ 1 mg/m³ MOLECULAR WEIGHT: 62.07
1,2-Ethanediol EG Ethylene alcohol Ethylene glycol Glycol alcohol Monoethylene glycol Permanent antifreeze		

REACTIVITY	The National Fire Protection Association reports that mixture of ethylene glycol with chlorosulfonic acid, oleum, or sulfuric acid causes the pressure and temperature to increase in a closed container. Reactions of glycols with non-oxidizing mineral acids typically generate heat, while those with oxidizing mineral acids, organic peroxides or hydroperoxides, or other strong oxidizing agents may evolve heat and fire. Compatibility charts further indicate that reactions of glycols with organic acids, isocyanates, or epoxides may initiate violent polymerization, while those with alkali or alkaline earth elemental metals or strong reducing agents may evolve heat, flammable gases and fire. Reactions with nitrides may produce heat, flammable gases, and an explosion (511, 505).

PHYSICO-CHEMICAL DATA	• Physical State: Liquid (at 20°C)	(54)
	• Color: Colorless	(2)
	• Odor: None	(23)
	• Odor Threshold: No data	
	• Density: 1.1135 g/mL (at 20°C)	(68)
	• Freeze/Melt Point: -13.00°C	(68)
	• Boiling Point: 197.60°C	(68)
	• Flash Point (°C): 111 (closed cup); 116 (open cup)	(23,60,506)
	• Flammable Limits: 3.20 to ? % by volume	(23,38,51)
	• Autoignition Temp.: 398.0 to 400.0°C or 413°C	(51,60,506)

PHYSICO-CHEMICAL DATA (Cont.)	• Vapor Pressure: 5.00E-02 mm Hg (at 20°C)	(67)
	• Satd. Conc. in Air: 3.4000E+02 mg/m³ (at 20°C)	(67)
	• Solubility in Water: Complete	(507)
	• Viscosity: 19.830 cp (at 20°C)	(21)
	• Surface Tension: 4.8400E+01 dyne/cm (at 20°C)	(59)
	• Log (Octanol-Water Partition Coeff.): -1.36	(29)
	• Soil Adsorp. Coeff.: 2.00E-02	(611)
	• Henry's Law Const.: 6.00E-08 (966) atm · m³/mol (at 25°C)	
	• Bioconc. Factor: 2.00E-03 (estim)	(659)

PERSISTENCE IN THE SOIL-WATER SYSTEM	Ethylene glycol is expected to be highly mobile in the soil/ground-water system. Sorption onto soil is weak and volatilization is expected to be minimal. Although data on biodegradation in soil are limited, ethylene glycol is not expected to be highly persistent.

PATHWAYS OF EXPOSURE	The primary pathway of concern from a soil/ground-water system is the migration of ethylene glycol to groundwater drinking water supplies, although no data confirm this. Inhalation or bioaccumulation of ethylene glycol are not likely to be important exposure pathways.

HEALTH HAZARD DATA	Signs and Symptoms of Short-term Human Exposure: (69) Clinical symptoms include CNS dysfunction with severe metabolic acidosis, cardiopulmonary failure and acute renal failure. Acute Toxicity Studies:(3504) INHALATION: TC_{Lo} 10000 mg/m³ Human ORAL: LD_{50} 7500 mg/kg Mouse LD_{Lo} 398 mg/kg Human LD_{50} 5500 mg/kg Dog LD_{50} 1650 mg/kg Cat LD_{50} 4700 mg/kg Rat LD_{Lo} 786 mg/kg Human SKIN: LD_{50} 9530 mg/kg Rabbit Long-Term Effects: CNS depression, severe renal damage, cardiopulmonary dysfunction Pregnancy/Neonate Data: Teratogenic Genotoxicity Data: Conflicting results Carcinogenicity Classification: IARC - None assigned NTP - Under study (histopathology in progress) EPA - Group D (not classifiable as to human carcinogenicity)
HANDLING PRECAUTIONS	NIOSH approved air-supplied respirator or other types in absence of proper environmental controls. Wear appropriate protective clothing and gloves (such as nitrile rubber). Chemical splash goggles to protect eyes.

ENVIRONMENTAL AND OCCUPATIONAL STANDARDS AND CRITERIA

AIR EXPOSURE LIMITS:

Standards
- OSHA TWA (8-hr): None established; Ceiling Limit: 50 ppm
- AFOSH PEL (8-hr TWA): None established; Ceiling Limit: 50 ppm

Criteria
- NIOSH IDLH (30-min): None established
- ACGIH CL: 50 ppm (vapor)
- ACGIH STEL (15-min): None established

WATER EXPOSURE LIMITS:

Drinking Water Standards
None established

EPA Health Advisories and Cancer Risk Levels (3977)
In the absence of formal drinking water standards, the EPA has developed the following Health Advisories which provide specific advice on the levels of contaminants in drinking water at which adverse health effects would not be anticipated.

- 1-day (child): 20 mg/L
- 10-day (child): 6 mg/L
- longer-term (child): 6 mg/L
- longer-term (adult): 20 mg/L
- lifetime (adult): 7 mg/L

WHO Drinking Water Guideline
No information available.

EPA Ambient Water Quality Criteria
- Human Health (355)
  - No criterion established; ethylene glycol is not a priority pollutant.
- Aquatic Life (355)
  - No criterion established; ethylene glycol is not a priority pollutant.

REFERENCE DOSES:

ORAL: 2.000E+00 mg/kg day (3744)

REGULATORY STATUS (as of 01-MAR-89)

Promulgated Regulations

- Federal Programs

  Comprehensive Environmental Response, Compensation and Liability Act (CERCLA)
  Under SARA Title III Section 313, manufacturers, importers, processors, and users of ethylene glycol must report annually to EPA and state officials their releases of this chemical to the environment (3787).

  Federal Insecticide, Fungicide and Rodenticide Act (FIFRA)
  Ethylene glycol is exempt from a tolerance requirement when used as an antifreeze or deactivator for all pesticides used before a crop emerges from the soil and for herbicides used before or after a crop emerges (315). Ethylene glycol is exempt from a tolerance requirement when used in foliar applications to peanut plants (314).

  Marine Protection Research and Sanctuaries Act (MPRSA)
  Ocean dumping of organohalogen compounds as well as the dumping of known or suspected carcinogens, mutagens or teratogens is prohibited except when they are present as trace contaminants. Permit applicants are exempt from these regulations if they can demonstrate that such chemical constituents are non-toxic and non-bioaccumulative in the marine environment or are rapidly rendered harmless by physical, chemical or biological processes in the sea (309).

  Occupational Safety and Health Act (OSHA)
  A ceiling level of 50 ppm ethylene glycol shall not be exceeded at any time during an 8-hour work-shift (3539).

  Food, Drug and Cosmetic Act (FDCA)
  Ethylene glycol is approved for use as an indirect food additive as a component of adhesives (3209).

  Consumer Product Safety Act (CPSA)
  Ethylene glycol-based radiator antifreeze distributed in containers intended or suitable for household use may be misbranded if they fail to bear a warning statement adequate for protection of the public health and safety (1236).

- State Water Programs

  ALL STATES

  All states have adopted EPA Ambient Water Quality Criteria and NPDWRs (see Water Exposure Limits section) as their promulgated state regulations, either by narrative reference or by relisting specific criteria. These states have promulgated additional or more stringent criteria:

  CONNECTICUT

  Connecticut has an action level of 100 μg/L for ethylene glycol in drinking water (3138).

  NEW HAMPSHIRE

  New Hampshire has set an enforceable Toxic Contaminant Level (TCL) for ethylene glycol in drinking water of 19 mg/L for a one-day exposure (assumes a child weighing 10 kg who drinks one liter of water per day) (3710).

  NEW YORK

  New York has an MCL of 50 μg/L for ethylene glycol in drinking water, and a nonenforceable water quality guideline of 50 μg/L for surface and ground-waters (3501).

  VERMONT

  Vermont has a preventive action limit of 3.5 mg/L and an enforcement standard of 7 mg/L for ethylene glycol in ground-water (3682).

Proposed Regulations

- Federal Programs

  No proposed regulations are pending.

- State Water Programs

  MOST STATES

  Most states are in the process of revising their water programs and proposing changes to their regulations which will follow EPA's changes when they become final. Contact with the state officers is advised. Changes are projected for 1989-90 (3683).

  MINNESOTA

  Minnesota has proposed a Recommended Allowable Limit (RAL) of 14,000 μg/L for drinking water (3451).

EEC Directives

Directive on Marketing and Use of Dangerous Substances (541)
Ethylene glycol may not be used in ornamental objects intended to produce light or color effects by means of different phases.

Directive Relating to the Classification, Packaging and Labeling of Dangerous Preparations (Solvents) (544)
Ethylene glycol is listed as a Class II/a harmful substances and is subject to packaging and labeling regulations.

Directive on the Classification, Packaging and Labeling of Dangerous Substances (787)
Ethylene glycol is classified as a harmful substance and is subject to packaging and labeling regulations.

EEC Directive-Proposed

Resolution on a Revised List of Second-Category Pollutants (545)
Ethylene glycol is one of the second-category pollutants to be studied by the Commission in the programme of action of the European Communities on Environment in order to reduce pollution and nuisances in the air and water. Risk to human health and the environment, limits of pollutant levels in the environment, and determination of quality standards to be applied will be assessed.

43.1 MAJOR USES

Ethylene glycol is a colorless, odorless, hygroscopic liquid infinitely soluble in water and many organic liquids. Due to its ability to markedly reduce the freezing point of water, about 40% of all ethylene glycol production goes to the manufacturing of nonvolatile antifreeze and liquid coolant for motor vehicles. Approximately 35% is used to manufacture polyester fiber and film. Ethylene glycol is also used in hydraulic fluids, as a solvent and as a heat transfer agent, especially in solar powered hot-water heaters (59, 507).

43.2 ENVIRONMENTAL FATE AND EXPOSURE PATHWAYS

43.2.1 Transport in Soil/Ground-water Systems

43.2.1.1 Overview

Ethylene glycol is expected to be highly mobile in the soil/ground-water system when present at relatively low concentrations or as a separate organic phase (resulting from a spill of significant quantities of the chemical). In general, transport pathways can be assessed by using an equilibrium partitioning model as shown in Table 43-1. These calculations predict the partitioning of low soil concentrations of ethylene glycol among soil particles, soil water and soil air. Portions of ethylene glycol associated with the water and air phases of soil have higher mobility than the sorbed portion.

Estimates for the unsaturated topsoil model indicate that only 0.4% of the ethylene glycol is expected to be sorbed onto soil particles. Approximately 99.6% is expected to partition to the mobile soil-water phase, and is thus available to migrate by bulk transport (e.g., the downward movement of infiltrating water), dispersion and diffusion. Since a very small portion of ethylene glycol is expected to be in the gaseous phase of the soil (less than 0.001%), diffusion through the soil-air pores up to the ground surface and subsequent removal by wind would appear to be a minor loss pathway. In saturated, deep soils (containing no soil air and negligible soil organic carbon), almost all of the ethylene glycol (99.99%) is predicted to be present in the soil-water phase (Table 43-1) and available for transport with flowing ground water. Sorption onto deep soils (less than 0.01%) is not expected to be significant. Overall, ground water underlying ethylene glycol-contaminated soils with low organic content is expected to be vulnerable to contamination.

TABLE 43-1
EQUILIBRIUM PARTITIONING CALCULATIONS FOR ETHYLENE GLYCOL IN MODEL ENVIRONMENTS[a]

Soil Environment	Estimated Percent of Total Mass of Chemical in Each Compartment		
	Soil	Soil-Water	Soil-Air
Unsaturated topsoil at 25°C[b,c]	0.4	99.6	7E-04
Saturated deep soil[d]	8E-03	99.99	-

a) Calculations based on Mackay's equilibrium partitioning model (34, 35, 36); see Introduction in Volume 1 for description of model and environmental conditions chosen to represent an unsaturated topsoil and saturated deep soil. Calculated percentages should be considered as rough estimates and used only for general guidance.
b) Utilized estimated soil sorption coefficient: K_{oc} = 0.02.
c) Henry's law constant taken as 6E-08 atm · m^3/mol at 25°C (966).
d) Used sorption coefficient K_p = 0.001 K_{oc}.

43.2.1.2 Sorption on Soils

The mobility of ethylene glycol in the soil/ground-water system (and its eventual migration into aquifers) is governed by the extent of its sorption on soil particles. Ethylene glycol is miscible in water and, as evidenced by its negative log K_{ow} and low K_{oc}, adsorption to soil/sediments is not expected to significantly influence its environmental fate.

Lokke (862) studied the adsorption and leaching of ethylene glycol in subsoils. No adsorption was observed for ethylene glycol (0.1-90 mg/L) onto two sandy soils and one clay subsoil ranging from 0.1-0.2% organic carbon. Leaching studies performed with soil cores of sandy till showed that ethylene glycol (150-220 g/L) closely followed the movement of water with little or no retardation.

43.2.1.3 Volatilization from Soils

Transport of ethylene glycol vapors through the air-filled pores of unsaturated soils may occur in near-surface soils. However, modeling results suggest that an insignificant fraction of the ethylene glycol loading will be present in the soil-air phase.

In general, important soil and environmental properties influencing the rate of volatilization include soil porosity, temperature, convection currents and barometric

pressure changes; important physicochemical properties include the Henry's law constant, the vapor-soil sorption coefficient, and, to the lesser extent, the vapor phase diffusion coefficient (31).

Data on ethylene glycol volatilization from soils, in particular, are not available. Ethylene glycol is not strongly sorbed to soil and is highly soluble in water. Although some volatilization may occur at the surface, the low value of the Henry's law constant (6E-08 atm · m^3/mole) suggests that vapor concentrations in soil will be low whenever water is present and volatilization will be minimal.

43.2.2 Transformation Processes in Soil/Ground-water Systems

No information was available on the non-biological degradation of ethylene glycol in the environment. Thermo-oxidative degradation to organic acids has been reported for ethylene glycol used as an antifreeze mixture (866).

A variety of studies have reported that ethylene glycol can be readily biodegraded under both aerobic and anaerobic conditions (867, 865, 868, 864, 869, 879). Data on degradation by microorganisms isolated from soil are contradictory. Harada and Nagashima (871) reported growth and nongrowth with ethylene glycol as the sole carbon source. Jensen (872) reported no degradation using microbes isolated from soil. Gaston and Stadtman (868) reported rapid degradation under anaerobic conditions using microbes isolated from mud.

Degradation using activated sludge microorganisms or sewage seed was rapid; complete degradation within a few days was reported in several studies (873, 874, 875, 876, 877, 878). Concentrations up to 2000 ppm were shown to support microbial growth, with an optimum concentration of 200 ppm reported. However, some concentrations above 1000 ppm were inhibitory (879); concentrations above 10,000 ppm inhibited growth of activated sludge (863).

In actual soil/ground-water systems, the concentrations of microorganisms capable of degrading ethylene glycol may be low, and may drop off with increasing depth; prediction of biodegradation rates in the environment is not possible. However, since both aerobic and anaerobic degradation have been demonstrated, persistence of ethylene glycol in environments with sufficient active microbial populations is not expected.

43.2.3 Primary Routes of Exposure from Soil/Ground-water Systems

The above discussion of fate pathways suggests that ethylene glycol is essentially nonvolatile, is very weakly sorbed to soil, and has little potential for bioaccumulation. These fate characteristics suggest several potential exposure pathways.

The potential for ground-water contamination with ethylene glycol is high, particularly in sandy soils. It has been detected in ground water associated with hazardous waste sites. Mitre (83) reported that ethylene glycol has been found in

1 of the 546 National Priority List (NPL) sites. At this particular site it was detected in surface water. However, it may not be commonly analyzed for at NPL sites as it is not a priority pollutant and is not commonly thought to be of concern to public health. The properties of ethylene glycol suggest that drinking water exposure from ground-water contamination is likely to be its primary route of exposure from soil/ground-water systems.

The movement of ethylene glycol in ground water may result in discharge to surface water. As a result, ingestion exposures may occur resulting from the use of surface waters as drinking water supplies, and dermal exposures may result from the recreational use of surface waters. Such exposures are likely to be lower than those from drinking contaminated ground water due to the degradation of ethylene glycol in surface water. Any pathways related to the uptake by aquatic organisms or domestic animals from surface waters are likely to be less significant than other sources of exposure due to the low BCF for ethylene glycol.

43.2.4 Other Sources of Human Exposure

Ethylene glycol is used in antifreeze, hydraulic fluids, electrolytic condensers, heat exchangers and as an industrial solvent. As such, there are likely to be a number of sources of human exposure; however, data documenting these exposures are lacking.

43.3 HUMAN HEALTH CONSIDERATIONS

43.3.1 Animal Studies

43.3.1.1 Carcinogenicity

No tumors were reported when ethylene glycol was injected subcutaneously into rats and mice for 2-15 months; the levels used were not cited (1034, 1035, 1036). Blood (1037) found no increased incidence of tumors in rats after being fed a diet containing 1% ethylene glycol for 2 years. Ethylene glycol is currently under investigation by the NTP to determine possible carcinogenic effects via dietary exposure (0047).

43.3.1.2 Mutagenicity

Ethylene glycol was found to be inactive in the TA-98, TA-100, TA-1535 and TA-1537 strains of Salmonella typhimurium (1017, 1038).

43.3.1.3 Teratogenicity, Embryotoxicity and Reproductive Effects

Maronpot et al. (1018) fed 80 pregnant Fischer 344 rats a diet containing 0, 0.04, 0.2, or 1 g/kg/day of ethylene glycol on days 6-15 of gestation. No maternal toxicity or increased incidence of teratogenic effects were observed at any of the dosage levels used. There was a statistically significant increase in delayed ossification (24% vs. 3% in control animals) and unossified (44% vs. 19% in control animals) vertebrae centra observed in fetuses of the dams that received 1 g/kg/day of ethylene glycol. These effects were attributed to delayed maturation and were considered evidence of minimal embryotoxicity.

Hardin et al. (3271) observed maternal and fetal toxicity when CD-1 mice were exposed by gavage to 10 mL/kg/day of undiluted ethylene glycol on gestational days 6-13. Statistically significant signs of maternal toxicity were an increase in maternal mortality, a reduction in weight gain and a reduction in viable litters. Fetal toxicity was demonstrated by significant reductions in liveborn/litter, percentage survival, birth weight and pup weight gain.

In a recent study, Lamb et al. (1019) continuously administered 0, 0.25, 0.5, or 1% ethylene glycol in the drinking water of male and female CD-1 mice. Mice from each treatment group were paired and allowed to mate. No treatment-related effects were observed on body weight or water consumption and no clinical signs of toxicity were evident in the parental generation. During a 14-week co-habitation period, exposure to 1% ethylene glycol in the drinking water was associated with a statistically significant decrease in the number of litters per fertile pair (4.5 vs. 4.9), the mean number of live pups per litter (10.2 vs. 10.8) and the mean live pup weight (1.53 vs. 1.63). The neonatal pups exhibited various malformations such as fused ribs, twisted spine, abnormally shaped or missing sternebrae, abnormally shaped vertebrae and cleft lip following continuous exposure of the parents to 1% (1.64 g/kg/day) ethylene glycol in the drinking water. No such defects were observed among control mice. The progeny of the F_1 generation, also continuously exposed to the 1% ethylene glycol drinking water, displayed modified craniofacial characteristics as adults which were not apparent in the neonatal period of growth. These facial abnormalities included a shortened snout and wide set eyes. Fertility in the F_1 generation was also decreased (61% vs. 80% in the control group).

Price et al. (1020) confirmed and expanded the results reported in the Lamb study (1019). Pregnant CD rats were dosed by gavage with 0, 1250, 2500, or 5000 mg/kg/day and CD-1 mice with 0, 750, 1500, or 3000 mg/kg/day of ethylene glycol on days 6-15 of gestation. No maternal deaths or distinctive clinical signs were noted; however, a significant dose-related decrease in maternal weight gain was observed at all levels in rats and at the 1500 and 3000 mg/kg/day levels in mice. Fetal body weight per litter was significantly reduced at the mid- and high-dosage levels in the rats and at all levels in the mice. The percentage of litters with malformed fetuses was significantly increased in all treatment groups and followed a dose-related trend. The most commonly observed malformations were cleft lip and palate, fused ribs, neural tube closure defects and abnormally shaped vertebrae and sternebrae. In

mice, two fetuses in one litter in the 3000 mg/kg/day treatment group each exhibited a mid-facial cleft, which is an unusual defect for the CD-1 species. The shortened frontal, nasal and parietal bones observed in the F_1 mice following continuous pre- and postnatal exposure to ethylene glycol (1019) were not observed in fetal rats or mice in this study.

Union Carbide (1021) reported results of a recent inhalation study on the teratogenic effects of ethylene glycol in CD rats and CD-1 mice. The duration of the study was not provided. A reduced ossification in the humerus, zygomatic arch and hind limb metatarsals and phalanges indicated slight fetotoxicity in rats exposed to 1000 or 2500 mg/m^3 ethylene glycol. CD-1 mice also exposed to 1000 or 2500 mg/m^3 ethylene glycol experienced reduced body weight and reduced ossification at numerous skeletal locations. Teratogenicity was demonstrated at both of these concentrations in mice as shown by a statistically significant increase of external, visceral and skeletal malformations. Predominant terata included exencephaly, cleft palate, abnormal faces and facial bones, fused vertebrae and abnormal ribs.

A possible mechanism of action for the teratogenic effects of ethylene glycol has been proposed by Lamb (1019). A metabolite of ethylene glycol, oxalic acid, is known to chelate calcium. Lamb suggests that this calcium chelation may lead to hypocalcemia and may act upon fetal development by altering the biological supply of the calcium cation.

43.3.1.4 Other Toxicologic Effects

43.3.1.4.1 Short-term Toxicity

Ingestion of ethylene glycol generally results in depression followed by respiratory and cardiac failure, renal damage and possibly brain damage (54). The oral LD_{50} for the rat is 4700 mg/kg and for the mouse is 7500 mg/kg (47). Inhalation of ethylene glycol primarily results in depression of the CNS and hematopoietic dysfunction but rarely results in death (54). No LC_{50} value was found in the literature for ethylene glycol. The dermal LD_{50} is listed as 9530 mg/kg in rabbits (47).

Typical signs of ethylene glycol poisoning are best exemplified in the dog. Dogs were orally given 6 mL ethylene glycol/kg body weight. Signs included incoordination, increased depth and rate of respiration and increased heart rate. As progression of the poisoning continued, collapse and labored breathing ensued. Coma and death occurred within 37 hours. Necropsy revealed pulmonary and gastric hyperemia, severe toxic tubular nephrosis and renal oxalosis (1022). One to three hours after feeding dogs 9.5 mL ethylene glycol/kg body weight, Grauer et al. (1023) observed depression, incoordination and increased fluid intake and urine output. Severe metabolic acidosis developed as the osmolal and anion gap increased. Within 6 hours, calcium oxalate crystalluria was observed, but it was not until 48 hours post-ingestion that a diminished renal excretory function was seen.

McDonald et al. (1046) injected 0.5 mL of 0, 0.004, 0.04, 0.4, 4, or 40% ethylene glycol solution into the corneal shelf of albino New Zealand rabbits. One treatment per day was given for 5 days. The 0.4% solution was found to be the highest concentration that was nontoxic and non-irritating. Irritation resulting from the 4 and 40% solutions consisted of swelling, discharge and conjunctival redness. All eyes returned to normal within 7 days of the last treatment. No evidence of systemic toxicity was observed.

The effect of ethylene glycol on brain function was tested in the male albino rat by Rajagopal (1024). Rats were given 10 mg/kg of a 50% aqueous solution of ethylene glycol by an intragastric tube. Urinary pH, blood pH and plasma bicarbonate levels all fell indicating a condition of metabolic acidosis. In response to the acidotic state, the renal distal tubular cells synthesized 332% more ammonia. The calcium oxalate deposition in the kidney and the oliguria caused a back diffusion of ammonia into the blood stream, resulting in a 497% increase in blood ammonia. The levels of brain amino acids (glutamate, GABA and glutamine) were altered in an attempt to detoxify the large amounts of ammonia entering the brain via the blood stream. The glutamate levels dropped 15.2% in order to utilize the ammonia to synthesize glutamine (which increased by 29.7%). The GABA level was reduced by 20.5%. This change in amino acid balance affected neurotransmission, and may be a possible explanation for the brain damage and even death seen in several cases of ethylene glycol toxicity.

43.3.1.4.2 Chronic Toxicity

The primary effect of repeated oral doses of ethylene glycol is kidney damage. Injury may occur even though oxalate crystals are not deposited in the kidney.

The effect of ethylene glycol on the kidney was studied by Roberts and Seibold (1047). Ethylene glycol was administered in levels ranging from 0.25-10% in the drinking water of several macaque species of monkeys. The left kidney was removed from all animals between days 6 and 13 of the experiment. Animals were sacrificed when they were uremic (the build-up of protein by-products in the blood due to inadequate kidney function) or dying. Seven out of ten animals received 15 mL/kg or more ethylene glycol. Five of these animals had deposition of calcium oxalate crystals in the proximal tubules. Tubular epithelium adjacent to the crystals was necrotic. Six animals were continued on the experiment for longer than 12 days. Three of these animals (ethylene glycol dose ranging from 33 to 137 mL/kg) had renal changes proportional to the dose given. Well-marked to extreme deposition of calcium oxalate crystals in the proximal tubules along with necrosis of epithelial cells were present. Monkeys given total doses of less than 15 mL/kg ethylene glycol developed mild glomerular damage, but no calcium oxalate crystals were present. This led Roberts and Seibold to speculate that ethylene glycol or its metabolic products other than oxalic acid are capable of causing renal damage. Deposition of calcium oxalate crystals was also found in tissues other than kidney. Three animals that were found in a dying state by day 31 of the experiment had oxalate crystals present in the walls of the cerebral vessels and adjacent tissues. This study concluded that high doses of

ethylene glycol causes nephrotoxic necrosis in the proximal tubules while low doses of ethylene glycol cause abnormal glomerular permeability.

Rats maintained on a diet containing 1 or 2% ethylene glycol developed calcium oxalate bladderstones and severe renal injury and degeneration (1039).

43.3.2 Human and Epidemiologic Studies

43.3.2.1 Short-term Toxicologic Effects

The primary route of exposure to ethylene glycol in humans is by accidental or deliberate ingestion. Ingestion of about 100 mL can be fatal (12). The effects of ethylene glycol poisoning usually appear in three distinct phases. The onset of the first stage begins approximately 30 minutes to 12 hours following ingestion and predominately affects the CNS. With small doses, the victim appears drunk, but without the odor of alcohol on the breath; with large doses, stupor, coma, convulsions and possible death occur within the first 24 hours. If the individual survives beyond the initial 12-24 hours, cardiopulmonary signs become prominent. This phase is characterized by tachypnea, cyanosis, pulmonary edema and possible death within the next 24 hours. The final stage primarily affects the renal system and includes such signs and symptoms as flank pain, metabolic acidosis and anuria. Death may occur as late as 17 days postingestion (12).

Acute levels of ethylene glycol in the human body may lead to various metabolic problems. A 24-year-old man deliberately ingested an unknown quantity of ethylene glycol. The victim developed pulmonary edema and a decreased pulmonary compliance that fit the criteria for the Adult Respiratory Distress Syndrome (ARDS). Although many deaths from ethylene glycol have been attributed to cardiopulmonary dysfunction, this case is unusual because it represents a respiratory dysfunction in the presence of normal cardiac function (1025).

Cieciura (1026) examined renal biopsies of five patients with acute ethylene glycol poisoning on days 5, 10, 16 and 22 of hospitalization. Extensive calcium oxalate and carbonate crystals were present in the glomerular interloop spaces of the kidney which exerted mechanical as well as toxic effects on the surrounding tissue. The crystals were shown to persist until 22 days postingestion.

Edelhauser et al. (1027) studied the effects of high concentrations of ethylene glycol on human corneas in culture. No damage to the corneal endothelium was reported when up to 5000 ppm ethylene glycol was applied directly on the cornea for 2 hours.

43.3.2.2 Chronic Toxicologic Effects

Chronic exposure to ethylene glycol is rare in humans. Symptoms are generally listed as anorexia, oliguria, nystagmus, lymphocytosis and loss of consciousness (54).

An unusual case of chronic ethylene glycol toxicity due to inhalation was reported by Troisi (1040, 1041). Thirty-eight women were exposed to a mixture containing 40% ethylene glycol, 55% boric acid and 5% ammonia at 105°C while working in an electrolytic condenser factory. Nine women suffered frequent attacks of unconsciousness 2-3 times a week. Fourteen women developed nystagmus (an involuntary rapid movement of the eye ball) and five showed an absolute lymphocytosis. The attacks ceased immediately once exposure to ethylene glycol vapor ceased.

43.3.3 Levels of Concern

The ACGIH (3005) has established a ceiling limit of 50 ppm for ethylene glycol. OSHA (3539) has set a ceiling level of 50 ppm ethylene glycol not to be exceeded during an 8-hour work-shift.

The EPA (3954) has developed health advisories for a 10-kg child of 20 mg/L for one-day exposure and 6 mg/L for longer-term exposure to ethylene glycol in drinking water. EPA has also developed a longer-term health advisory of 20 mg/L and a lifetime health advisory of 7 mg/L for a 70-kg adult.

43.3.4 Hazard Assessment

Ethylene glycol is not considered to be either a carcinogenic or mutagenic hazard. A chronic feeding study using rats fed 1% ethylene glycol in the diet produced no evidence of carcinogenic activity (1037). There are no data to indicate any mutagenic activity either.

Ethylene glycol has been shown to produce dose-related teratogenic effects in rats and mice when administered by gavage or via the drinking water (1019, 1020) as well as by inhalation (1037).

The principal hazard to humans appears to be associated with ingestion of large quantities of ethylene glycol. Depression of the central nervous system, serious renal injury and death may result from ingestion of about 100 mL (12). Early symptoms following ingestion are similar to alcoholic inebriation, but if untreated, can result in respiratory failure, convulsions, cardiovascular collapse and severe metabolic acidosis (12).

43.4 SAMPLING AND ANALYSIS CONSIDERATIONS

Determination of the concentration of ethylene glycol in soil and water requires collection of a representative field sample and laboratory analysis. Care is required to prevent losses during sample collection and storage. Soil and water samples should be collected in airtight containers with little or no headspace; analysis should be completed within 14 days of sampling. In addition to the targeted samples, quality

assurance samples such as field blanks, duplicates, and spiked matrices should be included in the analytical program.

Ethylene glycol is not included among the EPA-designated priority pollutants, and an EPA-approved procedure for the analysis of ethylene glycol is not available. However, the recommended analytical method for glycols (1142) is gas chromatography with flame ionization detection (GC/FID). Samples may either be directly injected onto the gas chromatographic (GC) column (aqueous and organic liquid samples) or they may first be extracted with an organic solvent (e.g., methylene chloride) and the concentrated extract injected onto the GC column (aqueous and solid samples). Detection of ethylene glycol is then accomplished by a flame ionization detector. A mass spectrometer using either electron impact (EI) or chemical ionization (CI) techniques may also be used to detect ethylene glycol.

A detection limit for ethylene glycol using these methods was not determined but would be in the range of µg/L for aqueous samples and µg/g for non-aqueous samples which have been extracted and in the range of ppm for samples which have been directly injected.

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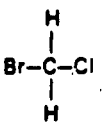
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COMMON SYNONYMS:	CAS REG.NO.: 74-97-5 FORMULA: CH_2BrCl NIOSH NO: PA5250000 STRUCTURE: 	AIR W/V CONVERSION FACTOR at 25°C (12) 5.3 mg/m³ ≈ 1 ppm; 0.189 ppm ≈ 1 mg/m³ MOLECULAR WEIGHT 129.40
Bromochloromethane CBM Chlorobromomethane Chloromethyl bromide Fluorocarbon 1011 Halon 1011 Methylene chlorobromide		

REACTIVITY	Reactions of halogenated organic materials such as bromochloromethane with cyanides, mercaptans or other organic sulfides typically generate heat, while those with mineral acids, amines, azo compounds, hydrazines, caustics, or nitrides commonly evolve heat and toxic or flammable gases. Reactions with oxidizing mineral acids may generate heat, toxic gases, and fires. Those with alkali or alkaline earth elemental metals, certain other chemically active elemental metals like aluminum, calcium, zinc or magnesium, organic peroxides or hydroperoxides, strong oxidizing agents, or strong reducing agents typically result in heat generation and explosions and/or fires (38, 54, 56).

PHYSICO-CHEMICAL DATA	• Physical State: Liquid (at 20°C)	(23)
	• Color: Colorless to pale yellow	(2)
	• Odor: Chloroform-like	(23)
	• Odor Threshold: 400.000 ppm	(384)
	• Density: 1.9344 g/mL (at 20°C)	(68)
	• Freeze/Melt Point: -86.50°C	(68)
	• Boiling Point: 68.10°C	(68)
	• Flash Point: Non-flammable	(23,38,51)
	• Flammable Limits: Non-flammable	(23,38,51)
	• Autoignition Temp.: Non-flammable	(23,38,51)

PHYSICO-CHEMICAL DATA (Cont.)	• Vapor Pressure: 1.17E+02 mm Hg (at 20°C) (38) • Satd. Conc. in Air: 8.3000E+05 mg/m³ (at 20°C) (1219) • Solubility in Water: 9.00E+03 mg/L (at 20°C) (38) • Viscosity: No data • Surface Tension: No data • Log (Octanol-Water Partition Coeff.): 1.41 (29) • Soil Adsorp. Coeff.: 1.20E+01 (611) • Henry's Law Const.: 1.22E-03 atm · m³/mol (at 20°C) (1219) • Bioconc. Factor: 5.00 (1219)

PERSISTENCE IN THE SOIL-WATER SYSTEM	Bromochloromethane is expected to be relatively mobile in surface soils and highly mobile in deep soils or sandy soils. Removal by volatilization is the primary loss pathway, particularly for material at the surface or in the soil-air phase. Transformation in natural soils is not expected to be significant.

PATHWAYS OF EXPOSURE	The primary exposure pathway of concern from soil/ground-water systems is the migration of bromochloromethane to groundwater drinking water supplies. Exposures through inhalation may be important in some situations, but ingestion of foods containing this compound is not generally expected to be significant.

HEALTH HAZARD DATA	Signs and Symptoms of Short-term Human Exposure: (38, 54) Bromochloromethane may cause irritation of the eyes and throat. Inhalation may cause disorientation, dizziness, headaches, anorexia, vomiting, abdominal pain, weight loss, memory impairment, paralysis, weakness, tremors, convulsions and narcosis. Prolonged contact may cause skin irritation. Acute Toxicity Studies: INHALATION: LC_{50} 12047 mg/m · 7 hr — Mouse (1297) ORAL: LD_{50} 5000 mg/kg — Rat (1297) LD_{50} 4300 mg/kg — Mouse (3504) Long-Term Effects: Reversible liver injury Pregnancy/Neonate Data: No data Genotoxicity Data: Conflicting in bacterium; negative in yeast Carcinogenicity Classification: IARC - No data NTP - No data EPA - No data
HANDLING PRECAUTIONS (38)	Handle chemical only with adequate ventilation • Vapor concentrations of 200-1000 ppm: any chemical cartridge respirator with an organic vapor cartridge • 1000-2000 ppm: any supplied-air respirator or self-contained breathing apparatus • 2000-5000 ppm: respirator with a chin-style or a front or back-mounted organic vapor canister • Chemical goggles if there is probability of eye contact • Appropriate clothing to prevent repeated or prolonged skin contact.

ENVIRONMENTAL AND OCCUPATIONAL STANDARDS AND CRITERIA

AIR EXPOSURE LIMITS:

Standards
- OSHA TWA (8-hr): 200 ppm
- AFOSH PEL (8-hr TWA): 200 ppm; STEL (15-min): 250 ppm

Criteria
- NIOSH IDLH (30-min): 5000 ppm
- ACGIH TLV® (8-hr TWA): 200 ppm
- ACGIH STEL (15-min TWA): deleted

WATER EXPOSURE LIMITS:

Drinking Water Standards
None established

EPA Health Advisories and Cancer Risk Levels
None established

WHO Drinking Water Guideline
No information available.

EPA Ambient Water Quality Criteria
- Human Health (355)
  - No criterion established; bromochloromethane is not a priority pollutant.
- Aquatic Life (355)
  - No criterion established; bromochloromethane is not a priority pollutant.

REFERENCE DOSES:
No reference dose available.

REGULATORY STATUS (as of 01-MAR-89)

Promulgated Regulations

- Federal Programs

Safe Drinking Water Act (SDWA)
Bromochloromethane is listed under the National Primary Drinking Water Regulations as an unregulated contaminant with no EPA monitoring requirements. The individual states decide which systems require analysis for this contaminant (3771).

Resource Conservation and Recovery Act (RCRA)
Effective July 8, 1987, the land disposal of untreated hazardous wastes containing halogenated organic compounds in total concentrations greater than or equal to 1000 mg/kg is prohibited. Effective August 8, 1988, the underground injection into deep wells of these wastes is prohibited. Certain variances exist until May, 1990 for some wastewaters and nonwastewaters for which Best Demonstrated Available Technology (BDAT) treatment standards have not been promulgated by EPA (3786). EPA requires that non-liquid hazardous wastes containing halogenated organic compounds (HOCs) in total concentrations greater than or equal to 1000 mg/kg or liquid hazardous wastes containing HOCs in total concentrations greater than or equal to 1% HOCs must be incinerated in accordance with the requirements of 40CFR264.343 or 265.343 (3782).

Toxic Substances Control Act (TSCA)
Manufacturers, importers and processors of bromochloromethane must submit health and safety studies on it to EPA (3789).

Marine Protection Research and Sanctuaries Act (MPRSA)
Ocean dumping of organohalogen compounds as well as the dumping of known or suspected carcinogens, mutagens or teratogens is prohibited except when they are present as trace contaminants. Permit applicants are exempt from these regulations if they can demonstrate that such chemical constituents are non-toxic and non-bioaccumulative in the marine environment or are rapidly rendered harmless by physical, chemical or biological processes in the sea (309).

Occupational Safety and Health Act (OSHA)
Employee exposure to bromochloromethane shall not exceed an 8-hour time-weighted average (TWA) of 200 ppm (3539).

Clean Air Act (CAA)
Although Fluorocarbon 1011 is given as a synonym for bromochloromethane, this chemical is not included on the list of fluorocarbons regulated as controlled substances under the Montreal Protocol for ozone depletion protection (3793).

Hazardous Materials Transportation Act (HMTA)
The Department of Transportation has designated bromochloromethane as a hazardous material subject to requirements

- State Water Programs

  ALL STATES

  All states have adopted EPA Ambient Water Quality Criteria and NPDWRs (see Water Exposure Limits section) as their promulgated state regulations, either by narrative reference or by relisting the specific numeric criteria. These states have promulgated additional or more stringent criteria:

  NEW YORK

  New York has set an MCL of 5 μg/L for bromochloromethane in drinking water (3501).

Proposed Regulations

- Federal Programs

  No proposed regulations are pending.

- State Water Programs

  NONE

  No proposed regulations are pending.

  MOST STATES

  Most states are in the process of revising their water programs and proposing changes to their regulations which will follow EPA's changes when they become final. Contact with state officers is advised. Changes are projected for 1989-90 (3683).

EEC Directives

Directive on Ground-Water (539)

Direct discharge into ground-water (i.e., without percolation through the ground or subsoil) of organophosphorous compounds, organohalogen compounds and substances which may form such compounds in the aquatic environment, substances which possess carcinogenic, mutagenic or teratogenic properties in or via the aquatic environment and mineral oils and hydrocarbons is prohibited. Appropriate measures deemed necessary to prevent indirect discharge into ground-water (i.e., via percolation through ground or subsoil) of these substances shall be taken by member countries.

Directive on the Quality Required of Shellfish Waters (537)
The mandatory specifications for organohalogenated and metal substances specify that the concentration of each substance in the shellfish water or in shellfish flesh must not reach or exceed a level which has harmful effects on the shellfish and larvae. The guideline specifications for organohalogenated substances or metals state that the concentration of each substance in shellfish flesh must be so limited that it contributes to the high quality of shellfish product.

Directive on the Discharge of Dangerous Substances (535)
Organohalogens, organophosphates, petroleum hydrocarbons, carcinogens or substances which have a deleterious effect on the taste and/or odor of human food derived from aquatic environments cannot be discharged into inland surface waters, territorial waters or internal coastal waters without prior authorization from member countries which issue emission standards. A system of zero-emission applies to discharge of these substances into ground-water.

Directive on Toxic and Dangerous Wastes (542)
Any installation, establishment, or undertaking which produces, holds and/or disposes of certain toxic and dangerous wastes including phenols and phenol compounds; organic-halogen compounds; chrome compounds; lead compounds; cyanides; ethers and aromatic polycyclic compounds (with carcinogenic effects) shall keep a record of the quantity, nature, physical and chemical characteristics and origin of such waste, and of the methods and sites used for disposing of such waste.

EEC Directives - Proposed
Proposal for a Council Directive on the Dumping of Waste at Sea (1793)
EEC has proposed that the dumping of organohalogen compounds at sea be prohibited.

Resolution on a Revised List of Second-Category Pollutants (545)
Bromochloromethane is one of the second-category pollutants to be studied by the Commission in the programme of action of the European Communities on Environment in order to reduce pollution and nuisances in the air and water. Risk to human health and the environment, limits of pollutant levels in the environment, and determination of quality standards to be applied will be assessed.

44.1 MAJOR USES

The major use of bromochloromethane is as a fire extinguisher fluid. Its effectiveness per unit weight makes it suitable for use in aircraft and portable extinguishers. It also has limited use as a chemical intermediate (12, 21).

44.2 ENVIRONMENTAL FATE AND EXPOSURE PATHWAYS

44.2.1 Transport in Soil/Ground-Water Systems

44.2.1.1 Overview

Bromochloromethane may be relatively mobile in the soil/ground-water system when present at low concentrations (dissolved in water and sorbed in soil) or as a separate organic phase (resulting from a spill of significant quantities of the chemical).

Transport pathways for low soil concentrations can be generally assessed by estimating equilibrium partitioning as shown in Table 44-1. These calculations predict the partitioning of bromochloromethane among soil particles, soil water and soil air. The estimates for the unsaturated topsoil model indicate that significant amounts (29%) of the bromochloromethane are expected to be present in the soil-water phase, and can thus migrate by bulk transport (e.g., the downward movement of infiltrating water), and dispersion and diffusion. A smaller portion (4.4%) is expected to partition to the soil-air phase; therefore, diffusion through the soil-air pores up to the ground surface, and subsequent removal by wind is a less significant transport pathway. In saturated, deep soils (containing no soil air and negligible soil organic carbon), a much higher fraction of the bromochloromethane (95%) is likely to be present in the soil-water phase and available for transport with flowing ground-water. Ground-water underlying bromochloromethane-contaminated soils with low organic content is particularly vulnerable to contamination.

44.2.1.2 Sorption on Soils

The mobility of bromochloromethane in the soil/ground water system (and its eventual migration into aquifers) is strongly affected by the extent of its sorption on soil particles. In general, sorption on soils is expected to:

- increase with increasing soil organic matter content;
- increase slightly with decreasing temperature;
- increase slightly with increasing salinity of the soil water; and
- decrease moderately with increasing dissolved organic matter content of the soil water.

TABLE 44-1
EQUILIBRIUM PARTITIONING CALCULATIONS FOR
BROMOCHLOROMETHANE IN MODEL ENVIRONMENTS[a]

Soil Environment	Estimated Percent of Total Mass of Chemical in Each Compartment		
	Soil	Soil-Water	Soil-Air
Unsaturated topsoil at 25°C[b,c]	66.7	28.9	4.4
Saturated deep soil[d]	4.8	95.2	-

a) Calculations based on Mackay's equilibrium partitioning model (34, 35, 36); see Introduction in Volume 1 for description of model and environmental conditions chosen to represent an unsaturated topsoil and saturated deep soil. Calculated percentages should be considered as rough estimates and used only for general guidance.
b) Used estimated soil sorption coefficient: K_{oc} = 12 (611).
c) Henry's law constant taken as 1.22E-03 atm · m^3/mol at 20°C (Arthur D. Little, Inc. estimate).
d) Used sorption coefficient (K_p) calculated as a function of K_{oc} assuming 0.1% organic carbon: $Kp = 0.001 \times K_{oc}$.

There are no available data on the extent of sorption of bromochloromethane on soils; data for other halomethanes indicate weak sorption. Schwarzenbach et al. (77) determined retardation rates, which represent interstitial water velocity/pollutant velocity ratios in the soil, for several chlorinated organics with higher K_{oc} values than bromochloromethane. The data indicate some retention in soils having 1-2% organic carbon content and little or no retention in soils with less than 0.1% organic carbon. Assuming analogous soil conditions, adsorption of bromochloromethane, particularly to deep soils, is not expected to be significant.

44.2.1.3 Volatilization from Soils

Transport of bromochloromethane vapors through the air-filled pores of unsaturated soils may occur, particularly in near-surface soils. In general, important soil and environmental properties influencing the rate of volatilization include soil porosity, temperature, convection currents and barometric pressure changes; important physico-chemical properties include the Henry's law constant, the vapor-soil sorption coefficient, and, to a lesser extent, the vapor phase diffusion coefficient (31). No

information is available on the latter two physico-chemical properties for bromochloromethane.

The Henry's law constant (H), which provides an indication of a chemical's tendency to volatilize from solution, is expected to increase significantly with increasing temperature; moderate increases in H were observed with increasing salinity and the presence of other organic compounds (18). The Henry's law constant for bromochloromethane is estimated to be 1.22E-03 atm.m^3/mol (Arthur D. Little, Inc. estimate) suggesting moderate to high volatilization from aqueous solution. Even though volatilization from soil will be lower than volatilization from water, it is expected to be a primary loss process for near-surface soils due to the weak sorption on soils and slow rate of transformation.

No specific information regarding the rate of volatilization of bromochloromethane from soils was available. Evidence of volatilization of bromochloromethane from river water has been reported (1644), although no rates were determined. Volatilization half-lives on the order of 20-90 minutes have been reported for chloromethane and dichloromethane in stirred aqueous solutions (10); half-lives for dibromochloromethane from rivers and streams have been reported to range from 43 minutes to 16.6 days. Since the vapor pressure of bromochloromethane (~120 torr) is less than that of dichloromethane (350 torr) but greater than that of dibromochloromethane (15 torr), the half-life of volatilization for bromochloromethane is expected to be intermediate between the above values. Volatilization of some halogenated organics from near-surface soils has been shown to be slower than their volatilization from well-stirred aqueous solutions by approximately one order of magnitude (82).

44.2.2 Transformation Processes in Soil/Ground-Water Systems

Data specific to the transformation of bromochloromethane in soil/ ground-water systems were not available. Maximum hydrolytic half-lives ranging from 137 years to 3000 years have been reported for other di- and tri-halomethanes (10), suggesting that hydrolysis in the environment is not expected to be significant. Photolysis and oxidation are also not expected to occur in the environment at rates significant enough to compete with volatilization.

Most references indicate that low molecular weight chloroaliphatics are not metabolized by microorganisms (10). However, Thom and Agg (80) have included several halomethanes in a list of organic chemicals amenable to degradation by biological sewage treatment, provided that suitable acclimation can be achieved. Tabak et al. (79) report significant degradation and rapid acclimation for bromochloromethane using an activated sludge population. In most soil/ground-water systems, however, the concentration of microorganisms capable of biodegrading chemicals such as bromochloromethane is very low and drops off sharply with increasing depth. Thus, biodegradation should be assumed to be of minimal importance except, perhaps, in landfills with active microbiological populations.

44.2.3 Primary Routes of Exposure from Soil/Ground-Water Systems

The above discussion of fate pathways suggests that bromochloromethane has a high volatility, is weakly sorbed, and has no significant potential for bioaccumulation. Bromochloromethane on the soil surface is likely to volatilize, but that portion not subject to volatilization is likely to be mobile in ground-water. These fate characteristics suggest several exposure pathways.

Volatilization of bromochloromethane from a disposal site could result in inhalation exposures. The potential for ground-water contamination is high, particularly in sandy soils. Mitre (83) reported that bromochloromethane has been found at 2 of the 546 National Priority List (NPL) sites. It was detected in the ground water at both of these sites. Among the available drinking water surveys of ground-water quality, bromochloromethane is not generally reported. It was detected, but not quantified, in the National Organics Monitoring Survey that was conducted in 1976-1977 (90). These data indicate that bromochloromethane is not a common contaminant in ground-water, probably due to its limited use. However, its properties, and information available on its fate, suggest that it should be mobile in soil/ground-water systems, and the contamination of drinking water would be of primary concern at sites where it is present.

Discharges of bromochloromethane to surface water from soil/ground-water systems would probably not represent significant sources of exposure due to the volatility and low potential for bioaccumulation of bromochloromethane.

44.2.4 Other Sources of Human Exposure

No other sources of exposure to bromochloromethane were identified.

44.3 HUMAN HEALTH CONSIDERATIONS

44.3.1 Animal Studies

44.3.1.1 Carcinogenicity

No carcinogenicity studies have been conducted with bromochloromethane.

44.3.1.2 Genotoxicity

Simmon et al. (1294) found bromochloromethane to be mutagenic in Salmonella typhimurium TA100. Osterman-Golkar et al. (3541) found it to be a strong positive in Salmonella strain TA100, a weak positive in TA1535, and negative in TA1950; they also declared it unequivocally positive in an Escherichia coli strain designed to detect reversions at the tyrosine locus, positive for inducing phage lambda in E. coli K39, and a weak positive for inducing mutations to streptomycin dependence in E. coli.

Another source noted a negative response in both Salmonella typhimurium and Saccharomyces cerevisiae D3 (1295).

44.3.1.3 Teratogenicity, Embryotoxicity and Reproductive Effects

No reproductive studies have been conducted with bromochloromethane.

44.3.1.4 Other Toxicologic Effects

44.3.1.4.1 Short-term Toxicity

Bromochloromethane appears to be one of the least toxic of the halomethanes; the primary response to overexposure is CNS depression (12). Oral LD_{50} values for rats and mice are 5000 mg/kg and 4300 mg/kg, respectively (1297, 47). Single oral doses of 1000 mg/kg or less have no apparent effect on rats, while single oral doses of 3000 and 4500 mg/kg caused fatty degeneration of the liver and kidneys in mice (12).

An LC_{50} of 2273 ppm for 7 hours has been reported for mice (1297). Concentrations of 3000 ppm produce light narcosis in rats within 15 minutes. Transient pulmonary edema was observed at concentrations below 27,000 ppm. Interstitial pneumonitis resulted in delayed deaths following exposure to 20,000 ppm. Deaths occurred during exposure only at concentrations above 27,000 ppm (1298).

When applied repeatedly to the open skin of rabbits, bromochloromethane produced moderate irritation and hyperemia; prolonged skin contact may cause dermatitis (46). A mean skin permeability constant of 0.79 cm/hr was calculated for rats exposed in a body-only chamber to vapor concentrations of 2500 to 40,000 ppm bromochloromethane for 4 hours. The total amount absorbed through the skin increased linearly with increasing vapor concentration at the skin surface (1299).

In rabbits, the liquid caused transient corneal epithelial injury and conjunctival edema (19).

44.3.1.4.2 Chronic Toxicity

Repeated inhalation of bromochloromethane causes little organic injury. Rats, rabbits and dogs exposed to a concentration of 1000 ppm, 7 hours daily, 5 days per week for 14 weeks showed no evidence of toxic response (1297). In another study, some liver pathology was observed in female rats and dogs exposed to 500 ppm in air for 6 months on the same dosing schedule. Rabbits, guinea pigs and male rats showed no effect at this level except elevated blood bromide levels. Histopathological changes in the liver and testes as well as elevated blood bromide levels were noted at 1000 ppm (1407).

44.3.2 Human and Epidemiologic Studies

44.3.2.1 Short-term Toxicologic Effects

There are few reports of adverse effects in humans from bromochloromethane exposure. This is probably due to its limited usage and low toxicity (12). Rutstein (1408) reported acute poisoning in three fire fighters exposed to unknown but very high vapor concentrations of bromochloromethane. Symptoms included severe headache, nausea and eye and throat irritation. Two of the three victims became comatose. Of these, one had convulsions, the other had respiratory arrest but was resuscitated. Recovery was slow but complete. Liver biopsies revealed normal microanatomy. Liver function studies were normal a few days after exposure.

Bromochloromethane is an irritant to the eyes and mucous membranes. Accidental discharge of a fire extinguisher close to the face produced immediate severe burning sensation in the eyes, followed by partial loss of the corneal epithelium. Discomfort and photophobia gradually subsided over the course of three days (19). Prolonged skin contact may cause dermatitis (46).

44.3.2.2 Chronic Toxicologic Effects

There are no data on the effects of chronic exposure, however, it does occur in manufacturing and packaging operations (2).

44.3.3 Levels of Concern

No water quality criteria or standards have been established to date regarding this chemical. The OSHA (3539) and ACGIH (3005) 8-hr TWA value is 200 ppm (1050 mg/m^3).

44.3.4 Hazard Assessment

The impact on human health resulting from either acute or long-term exposure to bromochloromethane has not been adequately evaluated in humans. Bromochloromethane vapor is a narcotic and respiratory irritant (12). The primary response to bromochloromethane exposure is CNS depression (e.g., mental confusion, dizziness, weakness, tremors). Prolonged or repeated skin contact may cause dermatitis (46). Eye contact can result in transient loss of corneal epithelium and photophobia (19).

Animal data provide little evidence of organic injury from either acute or chronic exposure to bromochloromethane. No effects were reported for rats, rabbits and dogs after repeated inhalation exposures to 1000 ppm for 14 weeks (1297), although another study indicated reversible liver pathology in rats (females only) and dogs but not rabbits, guinea pigs and male rats exposed to 500 ppm for six months under the same treatment regimen (1407).

No studies were found concerning the carcinogenic potential or reproductive effects associated with exposure to bromochloromethane. Two in vitro mutagenicity studies provide conflicting results in the Salmonella bacterium but negative results in the yeast, Saccaromyces cerevisiae. Additional studies are needed to clarify this issue. The potential impact on human health resulting from exposure to bromochloromethane cannot be clearly established at this time due to the extent and quality of health effects data available. However, based on limited data, bromochloromethane exposure does not appear to pose a major health hazard except at high vapor concentrations.

44.4 SAMPLING AND ANALYSIS CONSIDERATIONS

Determination of bromochloromethane concentrations in soil and water requires collection of a representative field sample and laboratory analysis. Due to the volatility of bromochloromethane, care is required to prevent losses during sample collection and storage. Soil and water samples are collected in airtight containers with no headspace; analysis should be completed within 14 days of sampling. However, recent studies (3430) show large losses of volatiles from soil handling. At the present, the best procedure is to collect the needed sample in an EPA VOA vial, seal with a foil-lined septum cap, and analyze the entire contents in the vial using a modified purge and trap apparatus. In addition to the targeted samples, quality control samples such as field blanks, duplicates, and spiked matrices should be included in the analytical program.

Bromochloromethane is not included among the EPA-designated priority pollutants and an EPA-approved procedure for the analysis of bromochloromethane is not available. However, EPA Methods 601, 624, 1624 (65), 8010, and 8240 (63) would be appropriate methods of choice for the analysis of bromochloromethane in aqueous samples. An inert gas is bubbled through the aqueous sample in a purging chamber at ambient temperature, transferring the bromochloromethane from the aqueous phase to the vapor phase and onto a sorbent trap. The trap is then heated and backflushed to desorb the bromochloromethane and transfer it onto a gas chromatographic (GC) column. The GC column is programmed to separate the volatile organics; bromochloromethane is then detected with a halide specific detector (Methods 601 and 8010) or a mass spectrometer (Methods 624, 1624, and 8240). For samples that contain high concentrations, direct injection may also be used. The generalized procedure for sample preparation for the analysis of volatile organics by purge and trap (Method 5030) (63) also recommends that samples be screened prior to the purge and trap step to prevent contamination of the system. The recommended screening techniques involve the analysis of a headspace sample by GC with photo-ionization or electrolytic conductivity detectors or the analysis of a solvent extract by GC with flame ionization or electrolytic conductivity detectors.

The EPA procedures (Methods 8010 and 8240) recommended for analysis of halogenated volatile organic compounds such as bromochloromethane in soil and waste samples (63), differ from the aqueous procedures primarily in the method by

which the analyte is introduced into the GC. The recommended method for low level samples (<1 mg/kg) involves dispersing the soil or waste sample in water and purging in a heated purge and trap device. The trap is desorbed and analyzed as described above. Recently introduced wide bore capillary columns show promise for increasing the performance of the GC analysis (3402, 3184, 3443).

Bromochloromethane detection limits for the various methods were not determined but would be in the range of 1-10 μg/L for aqueous samples and 1-10 μg/kg for non-aqueous samples.

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Note: The nonsequential numbers of the references reflect the order of references as they appear in the master bibliography.

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COMMON SYNONYMS:	CAS REG.NO.: 106-93-4 FORMULA: $C_2H_4Br_2$ NIOSH NO: KH9275000 STRUCTURE: $Br\text{-}CH_2\text{-}CH_2\text{-}Br$	AIR W/V CONVERSION FACTOR at 25°C (12) 7.68 mg/m³ ≈ 1 ppm; 0.13 ppm ≈ 1 mg/m³ MOLECULAR WEIGHT: 187.88
1,2-Dibromoethane EDB Ethylene dibromide Glycol dibromide		

REACTIVITY	Reactions of halogenated organic materials such as ethylene dibromide with cyanides, mercaptans or other organic sulfides typically generate heat, while those with amines, azo compounds, hydrazines, caustics, or nitrides commonly evolve heat and toxic or flammable gases. Reactions with oxidizing mineral acids may generate heat, toxic gases, and fires. Those with alkali or alkaline earth elemental metals, certain other chemically active elemental metals like aluminum, zinc or magnesium, organic peroxides or hydroperoxides, strong oxidizing agents, or strong reducing agents typically result in heat generation and explosions and/or fires. One source reports that ethylene dibromide slowly decomposes in the presence of light (light source unspecified) (38, 54, 56, 504).

PHYSICO-CHEMICAL DATA	• Physical State: Liquid (at 20°C)	(23)
	• Color: Colorless	(23)
	• Odor: Mildly sweet, chloroform odor	(60)
	• Odor Threshold: 10.000 ppm	(38)
	• Density: 2.1720 g/mL (at 20°C)	(21)
	• Freeze/Melt Point: 9.00°C	(23)
	• Boiling Point: 131.00°C	(23)
	• Flash Point: Non-flammable	(23,504)
	• Flammable Limits: Non-flammable	(23,504)
	• Autoignition Temp.: Non-flammable	(23,504,507)

PHYSICO-CHEMICAL DATA (Cont.)	• Vapor Pressure: 1.10E+01 mm Hg (at 20°C) (67) • Satd. Conc. in Air: 1.1300E+05 mg/m³ (at 20°C) (67) • Solubility in Water: 3.40E+03 mg/L (at 20°C) (21) • Viscosity: 1.676 cp (at 21°C) (60) • Surface Tension: 3.8750E+01 dyne/cm (at 20°C) (50) • Log (Octanol-Water Partition Coeff.): 1.76 (1645) • Soil Adsorp. Coeff.: 2.80E+01 (611) • Henry's Law Const.: 3.18E-04 atm · m³/mol (at 20°C) (74) • Bioconc. Factor: 2.70 (estim) (659)
PERSISTENCE IN THE SOIL-WATER SYSTEM	EDB is expected to be highly mobile in the soil/ground-water system. Adsorption onto soils, particularly soil of <1% organic content, is low. Volatilization may be an important transport process. Degradation of EDB in soil systems is not expected to be significant.
PATHWAYS OF EXPOSURE	The primary exposure pathway of concern from soil/ground-water systems is the migration of EDB to groundwater drinking water supplies. Inhalation exposures may also be important in some situations. Exposures through ingestion of foods contaminated with EDB from soil/ground-water systems are not generally expected to be significant.

HEALTH HAZARD DATA	Signs and Symptoms of Short-term Human Exposure: (38, 45, 54) Inhalation of EDB may cause irritation of the eyes, nose and throat. Systemic exposure via ingestion or inhalation can result in drowsiness, vomiting, nausea, abdominal pain, diarrhea and headache. Prolonged contact of the liquid with the skin may cause erythema, blisters and ulceration; these reactions may be delayed 24-48 hours. Acute Toxicity Studies: INHALATION: LC_{Lo} 3124 mg/m^3 · 2 hr Rat (47) ORAL: LD_{50} 108 mg/kg Rat (3504) SKIN: LD_{50} 300 mg/kg Rat (47) Long-Term Effects: Lung, liver and kidney damage Pregnancy/Neonate Data: Testicular injury Genotoxicity Data: Evidence of genotoxicity Carcinogenicity Classification: IARC - Group 2A (probably carcinogenic to humans) NTP - Positive evidence in rats EPA - Group B2 (probable human carcinogen; sufficient evidence in animals and inadequate evidence in humans)
HANDLING PRECAUTIONS (38,507)	Handle chemical only with adequate ventilation • Vapor concentrations of 20-400 ppm: any supplied-air respirator or self-contained breathing apparatus with full facepiece; chemical cartridge respirator with full facepiece and an organic vapor cartridge • Greater than 400 ppm: self-contained breathing apparatus with a full facepiece operated in pressure demand or other positive pressure mode • Chemical goggles if there is probability of eye contact • Neoprene or PVC gloves.

ENVIRONMENTAL AND OCCUPATIONAL STANDARDS AND CRITERIA

AIR EXPOSURE LIMITS:

Standards
- CSHA TWA (8-hr): 20 ppm; CL: 30 ppm; Peak: 50 ppm (5-min)
- AFOSH PEL (8-hr TWA): 20 ppm; CL: 30 ppm; Peak: 50 ppm (5-min)

Criteria
- NIOSH IDLH (30-min): Deleted; NIOSH has recommended that the substance be treated as a carcinogen
- NIOSH REL (8-hr TWA): 0.045 ppm; Ceiling Limit (15-min): 0.13 ppm
- ACGIH TLV® (8-hr TWA): avoid exposure (A2, suspected human carcinogen [skin])
- ACGIH STEL (15-min): none established

WATER EXPOSURE LIMITS:

Drinking Water Standards (3883)
MCLG: 0 µg/L (proposed)
MCL : 0.05 µg/L (proposed)

EPA Health Advisories and Cancer Risk Levels (3977)
The EPA has developed the following Health Advisories which provide specific advice on the levels of contaminants in drinking water at which adverse health effects would not be anticipated.

- 1-day (child): 8 µg/L
- 10-day (child): 8 µg/L
- 1E-04 cancer risk level: 0.04 µg/L

WHO Drinking Water Guideline
No information available.

EPA Ambient Water Quality Criteria
- Human Health (355)
  - No criterion established; ethylene dibromide is not a priority pollutant.
- Aquatic Life (355)
  - No criterion established; ethylene dibromide is not a priority pollutant.

REFERENCE DOSES:

No reference dose available.

REGULATORY STATUS (as of 01-MAR-89)

Promulgated Regulations

- Federal Programs

Clean Water Act (CWA)

Ethylene dibromide is designated a hazardous substance. It has a reportable quantity (RQ) limit of 454 kg (347, 3764). Ethylene dibromide is not listed as a toxic pollutant under the CWA (3770).

Safe Drinking Water Act (SDWA)

Ethylene dibromide is on the list of 83 contaminants required to be regulated under the SDWA of 1974 as amended in 1986 (3781). It is an unregulated contaminant requiring monitoring only for systems vulnerable to contamination by it (3771). In states with an approved Underground Injection Control program, a permit is required for the injection of ethylene dibromide-containing wastes designated as hazardous under RCRA (295).

Resource Conservation and Recovery Act (RCRA)

Ethylene dibromide is identified as a hazardous waste (U067) and listed as a hazardous waste constituent (3783, 3784). Waste streams from the organic chemicals industry (ethylene dibromide production) contain EDB and are listed as specific sources of hazardous waste (3774, 3765). Effective July 8, 1987, the land disposal of untreated hazardous wastes containing halogenated organic compounds in total concentrations greater than or equal to 1000 mg/kg is prohibited. Effective August 8, 1988, the underground injection into deep wells of these wastes is prohibited. Certain variances exist until May, 1990 for some wastewaters and nonwastewaters for which Best Demonstrated Available Technology (BDAT) treatment standards have not been promulgated by EPA (3786). EPA requires that non-liquid hazardous wastes containing halogenated organic compounds (HOCs) in total concentrations greater than or equal to 1000 mg/kg or liquid hazardous wastes containing HOCs in total concentrations greater than or equal to 1% HOCs must be incinerated in accordance with the requirements of 40CFR264.343 or 265.343 (3782). Ethylene dibromide is included on EPA's ground-water monitoring list. EPA requires that all hazardous waste treatment, storage, and disposal facilities monitor their ground-water for chemicals on this list when suspected contamination is first detected and annually thereafter (3775).

Comprehensive Environmental Response, Compensation and Liability Act (CERCLA)
Ethylene dibromide is designated a hazardous substance under CERCLA. It has a reportable quantity (RQ) limit of 454 kg. Reportable quantities have also been issued for RCRA hazardous waste streams containing ethylene dibromide but these depend upon the concentrations of the chemicals in the waste stream (3766). Under SARA Title III Section 313, manufacturers, processors, importers, and users of ethylene dibromide must report annually to EPA and state officials their releases of this chemical to the environment (3787).

Federal Insecticide, Fungicide and Rodenticide Act (FIFRA)
Tolerances have been established for inorganic bromide residues in or on raw agricultural commodities grown in soil treated with ethylene dibromide. Levels range from 5 to 125 ppm (977). Peanut hay and hulls containing inorganic bromide residues should not be represented, sold, or used as animal feed, as they contribute significantly to the level of inorganic bromides in meat and milk (314). The following tolerances have been established for residues of ethylene dibromide (1399):

- 0.001 ppm in or on soybeans
- 0.03 ppm in mangoes
- 0.9 ppm in barley, corn, oats, popcorn, rice, rye, sorghum, and wheat

Marine Protection Research and Sanctuaries Act (MPRSA)
Ocean dumping of organohalogen compounds as well as the dumping of known or suspected carcinogens, mutagens or teratogens is prohibited except when they are present as trace contaminants. Permit applicants are exempt from these regulations if they can demonstrate that such chemical constituents are non-toxic and non-bioaccumulative in the marine environment or are rapidly rendered harmless by physical, chemical or biological processes in the sea (309).

Occupational Safety and Health Act (OSHA)
Employee exposure to ethylene dibromide shall not exceed an 8-hour time-weighted average (TWA) of 20 ppm. A ceiling level of 30 ppm shall not be exceeded at any time during an 8-hour work-shift except for a duration of 5 minutes when it may reach a ceiling level of 50 ppm (3539).

Hazardous Materials Transportation Act (HMTA)
The Department of Transportation has designated ethylene dibromide as a hazardous material with a reportable quantity of 454 kg, subject to requirements for packaging, labeling and transportation (3180).

Food, Drug and Cosmetic Act (FDCA)
The following action levels have been established for residues of ethylene dibromide (1400): 150 ppb in milled products 30 ppb in finished (ready-to-eat) consumer products

- State Water Programs

ALL STATES
All states have adopted EPA Ambient Water Quality Criteria and NPDWRs (see Water Exposure Limits section) as their promulgated state regulations, either by narrative reference or by relisting the specific numeric criteria. These states have promulgated additional or more stringent criteria:

CALIFORNIA
California has set an MCL and an action level of 0.02 μg/L for ethylene dibromide in drinking water (3096, 3098).

CONNECTICUT
Connecticut has set an MCL of 0.1 μg/L for ethylene dibromide in drinking water (3137).

FLORIDA
Florida has an MCL of 0.02 μg/L for ethylene dibromide in drinking water (3219).

NEW MEXICO
New Mexico has a water quality criterion of 0.1 μg/L for ground-water (3499).

NEW YORK
New York has an MCL of 5 μg/L for ethylene dibromide in drinking water (3501).

SOUTH DAKOTA
South Dakota requires ethylene dibromide to be nondetectable, using designated test methods, in ground-water (3671).

VERMONT, WISCONSIN
Vermont and Wisconsin both have preventive action limits of 0.001 μg/L and enforcement standards of 0.01 μg/L for ethylene dibromide in ground-water (3682, 3840).

Proposed Regulations

- Federal Programs

  Safe Drinking Water Act (SDWA)

  EPA will propose a maximum contaminant level (MCL) of 0.05 µg/L and repropose a maximum contaminant level goal (MCLG) of zero for ethylene dibromide in May, 1989, with final action scheduled for December, 1989 (3751).

  Occupational Safety and Health Act (OSHA)

  OSHA has proposed lowering the employee exposure limits to ethylene dibromide. They have proposed an 8-hour time-weighted average of 0.1 ppm and a ceiling limit of 0.5 ppm. Requirements for exposure monitoring, methods of control, personal protective equipment, hygiene practices, medical surveillance and employee training and education have also been proposed. Final action on this standard is scheduled for December, 1989 (1394).

- State Water Programs

  MOST STATES

  Most states are in the process of revising their water programs and proposing changes to their regulations which will follow EPA's changes when they become final. Contact with the state officer is advised. Changes are projected for 1989-90 (3683).

  MINNESOTA

  Minnesota has proposed a Recommended Allowable Limit (RAL) of 0.005 µg/L for drinking water (3451).

EEC Directives

Directive Relating to the Quality of Water for Human Consumption (540)
The maximum admissible concentration for ethylene dibromide is 0.1 μg/L. The total maximum allowable concentration for pesticides and related products is 0.5 μg/L.

Directive on Ground-Water (533)
Direct discharge into ground-water (i.e., without percolation through the ground or subsoil) of organophosphorous compounds, organohalogen compounds and substances which may form such compounds in the aquatic environment, substances which possess carcinogenic, mutagenic or teratogenic properties in or via the aquatic environment and mineral oils and hydrocarbons is prohibited. Appropriate measures deemed necessary to prevent indirect discharge into ground-water (i.e., via percolation through ground or subsoil) of these substances shall be taken by member countries.

Directive on the Quality Required of Shellfish Waters (537)
The mandatory specifications for organohalogenated substances and metals specify that the concentration of each substance in the shellfish water or in shellfish flesh must not reach or exceed a level which has harmful effects on the shellfish and larvae. The guideline specifications for organohalogenated substances and metals state that the concentration of each substance in shellfish flesh must be so limited that it contributes to the high quality of shellfish product.

Directive Relating to the Classification, Packaging and Labeling of Dangerous Preparations (Solvents) (544)
Ethylene dibromide is listed as a Class I/a toxic substance and is subject to packaging and labeling regulations.

Directive on the Discharge of Dangerous Substances (535)
Organohalogens, organophosphates, petroleum hydrocarbons, carcinogens or substances which have a deleterious effect on the taste and/or odor of human food derived from aquatic environments cannot be discharged into inland surface waters, territorial waters or internal coastal waters without prior authorization from member countries which issue emission standards. A system of zero- emission applies to discharge of these substances into ground-water.

Directive on Marketing and Use of Dangerous Substances (541)
Ethylene dibromide may not be used in ornamental objects intended to produce light or color effects by means of different phases.

Directive on Toxic and Dangerous Wastes (542)
Any installation, establishment, or undertaking which produces, holds and/or disposes of certain toxic and dangerous wastes including phenols and phenol compounds; organic-halogen compounds; chrome compounds; lead compounds; cyanides; ethers and aromatic polycyclic

compounds (with carcinogenic effects) shall keep a record of he quantity, nature, physical and chemical characteristics and origin of such waste, and of the methods and sites used for disposing of such waste.

Directive on the Classification, Packaging and Labeling of Dangerous Substances (787)
Ethylene dibromide is classified as a toxic substance and is subject to packaging and labeling regulations.

Directive on Major Accident Hazards of Certain Industrial Activities (1794)
Ethylene dibromide manufacturers are required to incorporate preventive measures into the design of the manufacturing process and to consider possible causes of a major accidents, monitor processes at critical points, anticipate events which may lead to disaster, and introduce stringent safety measures. If a accident occurs a national competent authority should be notified if it is stored or processed in quantities in excess of 50 tons. Authorities must be provided with the circumstances of the accident, substances involved, emergency measures taken, and the data available for assessing the effects on man and the environment.

EEC Directives - Proposed
Proposal for a Council Directive on the Dumping of Waste at Sea (1793)
EEC has proposed that the dumping of organohalogen compounds at sea be prohibited. EEC has proposed that the dumping of pesticides at sea be forbidden without prior issue of a special permit. Dumping areas shall be designated in the permit.

Directive on the Approximation of the Laws. Regulations and Administrative Provisions Relating to the Classification, Packaging and Labeling of Dangerous Preparations (3991)
The lables on packages containing preparations classified as very toxic, toxic or corrosive must bear the safety advice S1/S2 and 346 in addition to the specific safety advice. If it is physically impossible to give such information, the package must be accompanied by precise and easily understood instructions.

Proposal for a Council Directive Amending Directive 79/117/EEC Prohibiting the Placing on the Market and Use of Plant Protection Products Containing Certain Active Substances (1427)
EEC has proposed that plant protection products containing ethylene dibromide not be placed on the market or used unless necessary because of an unforeseeable danger threatening plant production which cannot be controlled by other means, such products may be permitted to be marketed and/or used for a maximum period of 120 days.

45.1 MAJOR USES

The major use of ethylene dibromide (EDB) is as a lead scavenger in antiknock mixtures added to gasolines. Due to EPA regulations limiting the lead content of gasolines, the use of EDB in this area is decreasing. The second major commercial use of EDB has been as an ingredient of soil and grain fumigants to protect stored grain from pest infestations and to control fruit flies; however, recent EPA regulations have eliminated about 97% of EDB's agricultural use. The minor uses of EDB include use as a chemical intermediate and as a nonflammable solvent for resins, gums and waxes (1605).

45.2 ENVIRONMENTAL FATE AND EXPOSURE PATHWAYS

45.2.1 Transport in Soil/Ground-Water Systems

45.2.1.1 Overview

EDB, may move through the soil/ground-water system when present at low concentrations (dissolved in water and sorbed on soil) or as a separate organic phase (resulting from a spill of significant quantities of the chemical). In general, transport pathways can be assessed with the results of an equilibrium partitioning model as shown in Table 45-1. These calculations predict the partitioning of low soil concentrations of EDB among soil particles, soil water and soil air. The EDB associated with the water and air phases of the soil is more mobile than that which is adsorbed.

The estimates for the unsaturated topsoil model indicate that approximately 15% of the EDB is expected to be present in the soil-water phase and thus available to migrate by bulk transport (e.g., the downward movement of infiltrating water), dispersion and diffusion. For the small portion of EDB in the gaseous phase of the soil (1%), diffusion through the soil-air pores up to the ground surface, and subsequent removal by wind, may be a significant loss pathway. In saturated, deep soils (containing no soil air and negligible soil organic carbon), a much higher fraction of the EDB (89%) is expected to be in the soil-water phase (Table 45-1) and transported with flowing ground water. Ground water underlying EDB-contaminated soils with low organic content is highly vulnerable to contamination. Using an index designed to rank chemicals in terms of their relative potential to intrude into groundwater, Rao et al. (1531) determined that EDB had the highest potential for ground water contamination of the 41 organic chemicals they examined. Application of a screening model (808) to determine the behavior of trace organics in soil indicated that EDB is expected to be highly mobile by both diffusion and dispersion. Volatilization is expected to be significant with an effective half-life of 3.4 days under conditions of deep placement (10 cm) in soil containing 1.25% organic carbon.

TABLE 45-1
EQUILIBRIUM PARTITIONING CALCULATIONS FOR ETHYLENE DIBROMIDE IN MODEL ENVIRONMENTS[a]

Soil Environment	Estimated Percent of Total Mass of Chemical in Each Compartment		
	Soil	Soil-Water	Soil-Air
Unsaturated topsoil at 25°C[b,c]	83.8	15.6	0.6
Saturated deep soil[d]	10.5	89.5	-

a) Calculations based on Mackay's equilibrium partitioning model (34, 35, 36); see Introduction in Volume 1 for description of model and environmental conditions chosen to represent an unsaturated topsoil and saturated deep soil. Calculated percentages should be considered as rough estimates and used only for general guidance.
b) Use estimated soil sorption coefficient: K_p = 28 (611).
c) Henry's law constant taken as 3.18E-04 atm · m^3/mol at 25°C (74).
d) Used sorption coefficient K_p calculated as a function of K_{oc} assuming 0.1% organic carbon: $K_p = 0.001 \times K_{oc}$.

45.2.1.2 Sorption on Soils

The mobility of EDB in the soil/ground-water system (and its eventual migration into aquifers) is strongly affected by the extent of its sorption on soil particles. In general, sorption on soils is expected to:

- increase with increasing soil organic matter content;
- increase slightly with decreasing temperature;
- increase moderately with increasing salinity of the soil water; and
- decrease moderately with increasing dissolved organic matter content of the soil water.

Values of the equilibrium soil sorption constant (K_{oc}) for EDB have been reported to range from 28 to 66 (1531, 611, 230, 808, 1645) suggesting weak sorption to soils; sorption is expected to increase as organic content of the soil increases. Chiou et al. (1646) examined the transfer of nonionic chemicals, including EDB, from water to soil and indicated that the process is essentially one of partitioning (dissolution) rather than physical adsorption. The soil-water equilibrium isotherms showed no indication of curvature even at high concentrations, and the distribution coefficients were inversely proportional to the water solubilities.

Rogers and MacFarlane (1645) found only minimal sorption of EDB on soils (1.8-2.6% organic carbon content) and clay; only 0.3% to 4% of the available chemical was sorbed by the absorbent. Schwarzenbach et al. (77) determined retardation rates, which represent interstitial water velocity/ pollutant velocity in the soil, for several chlorinated organics with higher K_{ow} and K_{oc} values than EDB. The data indicate some retention in soils having 1-2% organic carbon content and little or no retention in soils with less than 0.1% organic carbon. Wilson et al. (82) reported a retardation factor of 1.2 in sandy soil for 1,2-dichloroethane with K_{ow} and K_{oc} values only slightly lower than those for EDB. Assuming analogous soil conditions, retention of EDB, particularly in deep soils of low organic content, is not expected to be significant.

45.2.1.3 Volatilization from Soils

Transport of EDB vapors through the air-filled pores of unsaturated soils may be an important transport mechanism for near-surface soils. In general, important soil and environmental properties influencing the rate of volatilization include soil porosity, temperature, convection currents and barometric pressure changes; important physicochemical properties include the Henry's law constant, the vapor-soil sorption coefficient, and to a lesser extent, the vapor phase diffusion coefficient (31). No information was available on the latter two physico-chemical properties.

The Henry's law constant (H), which provides an indication of a chemical's tendency to volatilize from solution, is expected to increase significantly with increasing temperature. Moderate increases in H were also observed with increasing salinity and the presence of other organic compounds (18). The Henry's law constant for EDB is estimated to be 3.18E-04 atm · m^3/mol (74), suggesting moderate volatility from aqueous solution. Although volatilization from soil will be slower than from water, it may be an important fate process due to the relatively weak sorption and slow transformation of EDB.

No specific information regarding the rate of EDB volatilization from soils was available. However, evidence of EDB emanating from selected hazardous and sanitary landfills in New Jersey has been provided (1647); ambient air concentrations in the vicinity of the hazardous waste sites were higher than levels measured at an urban/industrial site in Newark. No volatilization rates were determined.

Volatilization of EDB from water has been shown to be enhanced by subwater mixing (1597); the evaporation half-life from 1.6 cm of water with stirring was reported to be 6.8 minutes. Other studies have reported EDB volatilization half-lives ranging from 4-6 hours for 1 m water depth (1649). Volatilization half-lives for ethylene dichloride (1,2-dichloroethane), with a Henry's law constant of 1.1E-03 atm · m^3/mol, in stirred aqueous solutions have been reported to range from 29-90 minutes depending on the degree of agitation (10); volatilization of EDB from similar aqueous solutions would be somewhat slower. Compared to their volatilization from

well-stirred solutions, volatilization of some halogenated organics from near-surface soils has been reported to be slower by approximately one order of magnitude (82).

45.2.2 Transformation Processes in Soil/Ground-Water Systems

The persistence of EDB in soil/ground-water systems is not well documented. Under normal environmental conditions, EDB is not expected to undergo rapid hydrolysis. The half-life of EDB due to hydrolysis has been reported to be 5-10 days, favored by acid conditions (1650); other authors report the rate of hydrolysis in neutral water to be quite slow, with half-lives on the order of 13-16 years (1651, 1652). In soil-water culture, 0.1 mM EDB required two months for degradation (1651).

EDB has been shown to undergo rapid photohydrolysis in aqueous solution (1652) in spite of the fact that the absorption spectrum for EDB trails only slightly into the visible. The photolytic reaction of EDB (0.01 M) was complete within two hours, representing a rate enhancement on the order of 10^5 over the nonphotolytic pathway for which the half-life was determined to be 16 years. No additional data on the photolysis or oxidation of EDB in soil were available.

Literature references to microbial degradation of EDB are few. One study reported no degradation of EDB in water under anaerobic conditions in the presence of primary sewage seed (1653), while another study reported degradation under methanogenic conditions but no degradation in aerobic cultures (1654). Castro and Belser (1655) reported 97% degradation of EDB in eight weeks with a soil inoculum added to autoclaved soil.

Most references indicate that low molecular weight chloroaliphatics are not rapidly metabolized in the environment (76) although biodegradation by acclimated populations may occur. Slow to moderate degradation of ethylene dichloride was observed by Tabak et al. (79) with an acclimated, activated-sludge population; and Thom and Agg (80) included ethylene dichloride in a list of organic chemicals amenable to degradation by biological sewage treatment, providing suitable acclimatization was achieved. In situ biodegradation by blended specialized bacterial seed cultures has been suggested as a decontamination procedure for soils contaminated with ethylene dichloride (650). There are insufficient data to determine whether EDB would behave similarly.

In most natural soil/ground-water systems, the concentration of microorganisms capable of biodegrading chemicals such as EDB is expected to be very low and to drop off sharply with increasing depth. Thus, biodegradation in the soil/ground-water system should be assumed to be of minimal importance except, perhaps, in landfills with active microbiological populations.

45.2.3 Primary Routes of Exposure from Soil/Ground-Water Systems

The above discussion of fate pathways suggests that ethylene dibromide has a moderate volatility, is weakly sorbed to soil, and has no significant potential for bioaccumulation. Ethylene dibromide on the soil surface is likely to volatilize, but that portion not subject to volatilization is likely to be mobile in ground water. These fate characteristics suggest several exposure pathways.

Volatilization of EDB from a disposal site could result in inhalation exposures. Harkov et al. (1647) measured VOC (Volatile Organic Compounds) levels at six abandoned hazardous waste sites, as well as a sanitary landfill, in New Jersey. They found mean levels of EDB ranging from 0.01 to 0.47 ppb (volume) for the seven sites, with a maximum concentration of 6.71 ppb (volume). EDB was not detected (at about 0.05 ppb (volume)) at an urban/industrial site in Newark, New Jersey. The authors concluded that some VOC, including EDB were found at higher concentrations at hazardous waste sites than in typical urban areas.

The potential for drinking water contamination resulting from the migration of EDB with ground water is high. In a monitoring study of pesticides in ground water, EDB was detected at levels of 0.05 to 20 ppb (1797). In addition, EDB has been detected in a number of states. In one state, levels of EDB from 0.02-560 µg/L were detected in 25 samples of ground-water (992). While those levels are generally attributed to agricultural practices, the data indicate the mobility of EDB and its potential for contamination of ground-water drinking water supplies.

Discharges of EDB to surface water from soil/ground-water systems would probably not represent significant sources of exposure due to this compound's high volatility and its low potential for bioaccumulation.

45.2.4 Other Sources of Human Exposure

EDB has been widely used in the past as an additive in leaded gasoline as well as a pesticide.

As a result, there are a number of other sources of human exposure. As discussed in the previous section, EDB has been found to some extent in ground-water drinking water supplies. According to EPA (1419), levels in drinking water range from 0-560 µg/L. As a result of the use of EDB as a soil fumigant and as a postharvest fumigant, residues of this compound in food were common, although most uses of EDB were cancelled in 1984. In the EPA Position Document 4 (1796), they estimate the EDB intake from citrus to be 0.00041 mg/kg/day for non-California citizens, and 0.0069 mg/kg/day for California residents. The mean dietary intake from EDB-contaminated grain was estimated to be 0.0063 mg/kg/day. It is likely that these intakes may have decreased since uses of EDB are now limited.

EDB has been detected in air resulting from its use in leaded gasoline. Brodzinsky and Singh (84) conducted an assessment of available data for volatile organic chemicals. They reported median levels of EDB below detection limits in rural/remote areas, 200 ng/m^3 in urban/suburban areas, and 1500 ng/m^3 in source-dominated areas. A total of 930 data points were evaluated.

45.3 HUMAN HEALTH CONSIDERATIONS

45.3.1 Animal Studies

45.3.1.1 Carcinogenicity

EDB has been demonstrated to be carcinogenic in rodents by oral, inhalation and dermal routes.

The NCI conducted a bioassay of technical grade EDB by the oral route using Osborne-Mendel rats and B6C3F$_1$ mice (1606). EDB was administered in corn oil by gavage at time-weighted average doses of 41 or 38 mg/kg/day for male rats, 39 or 37 mg/kg/day for female rats, and 107 or 62 mg/kg/day for mice of both sexes. Due to excessive mortality, male and female rats were terminated in weeks 49 and 61, respectively, and all male and high dose female mice died or were sacrificed by week 78. In rats, squamous cell carcinomas of the forestomach were observed in a dose-related manner in both sexes at incidences ranging from 58 to 90%. Squamous cell carcinomas were also observed in both sexes of mice at incidences of 56 to 94%. None were found in controls of either species. These lesions were seen as early as week 12 in rats and week 24 in mice. There also were statistically significant incidences of hepatocellular carcinomas in female rats, hemangiosarcomas in male rats, and alveolar/bronchiolar adenomas in male and female mice.

A 78 to 103 week inhalation bioassay was conducted in F344 rats and B6C3F$_1$ mice under the National Toxicology Program (1743). Animals of both sexes in each species were exposed to vapor levels of either 10 or 40 ppm, 6 hours per day, 5 days per week. In rats, there was a dose-related increase in the incidence of nasal cavity tumors in both sexes (68%-86%). In high-dose animals of both sexes, there was a statistically significant increase in circulatory system hemangiosarcomas - 30% in males, 10% in females, none in controls. In high-dose males, there was a 50% incidence of mesotheliomas of the tunica vaginalis compared with none in the controls. In females, the incidence of fibroadenomas of the mammary gland was statistically significant in both low- and high-dose groups - 58% and 48%, respectively. There was 8% incidence in female controls. An 11% incidence of alveolar/ bronchiolar adenomas and carcinomas was also observed in high-dose females.

In mice a statistically significant number of alveolar/bronchiolar carcinomas and adenomas were seen in high-dose males (50%) and females (82%). There was an overall incidence of 4% in controls. Fibroadenomas of the mammary gland were seen in the females but the trend was not dose-related (28% in the low-dose group vs.

16% in the high-dose group). Hemangiosarcomas occurred in low- (22%) and high-dose (46%) females. There was also a 22% incidence of subcutaneous fibrosarcomas and a 24% incidence of nasal cavity carcinomas in high-dose females (1743).

Another inhalation study was conducted by Wong et al. (1744) in Sprague-Dawley rats. Animals were exposed to vapor concentrations of 20 ppm with and without 0.05% disulfiram in the diet or to disulfiram alone. Disulfiram decreases oxidative metabolism and increases the degree of glutathione conjugation of EDB, resulting in increased binding to DNA (1762). Exposure was for 7 hours per day, 5 days per week over an 18 month period. Survival of the animals was poor. At the end of 18 months, males and females exposed to EDB alone had mortalities of 90% and 77%, respectively. All animals receiving EDB and disulfiram died within 15 months. Male rats receiving EDB alone had significantly higher tumor incidences in the spleen, adrenal and subcutaneous mesenchymal tissue than control males. Females exposed to EDB had significantly higher tumor incidences in the spleen, adrenals and mammary glands when compared with female controls. In animals receiving EDB with disulfiram there were significant increases in tumors of the liver, kidneys and thyroid when compared with animals receiving EDB or disulfiram alone. There were also high incidences of hemangiosarcoma in the liver, spleen and mesentery in animals receiving the EDB/disulfiram combination. Males receiving the combination had a higher incidence of lung tumors than males receiving EDB alone. No lung tumors were observed in either control or disulfiram treated rats. Generally, in rats receiving the combination treatment, neoplasms were found earlier and at a higher incidence than in rats receiving either chemical alone.

Van Duuren et al. (142) found that EDB induced a statistically significant incidence of skin papillomas, skin carcinomas and lung tumors in female Ha:ICR Swiss mice. EDB was applied to the dorsal skin 3 times weekly as a 50 mg dose in 0.2 mL of acetone. The first tumor was seen after 395 days.

Kowalski et al. (1763) demonstrated that the target tissues for EDB-induced carcinogenic effects can metabolize EDB to reactive products which become universally bound to tissue constituents. A good correlation was found between reported organ sensitivities to EDB and the binding of EDB metabolites in the tissues. For example, a high degree of binding was found in the squamous epithelium of the forestomach, the bronchiolar epithelium, nasal epithelium and in the adrenal cortex, areas in which EDB has induced tumors in animals.

45.3.1.2 Genotoxicity

EDB is genotoxic to bacteria, fungi, insects and cultured mammalian cells in the absence of an activation system.

Reverse mutations have been reported in various strains of Salmonella typhimurium (1108, 1725), E. coli (1108) and B. subtilis (1725). In fungi, EDB produced forward mutations in Streptomyces coelicolor and Aspergillus nidulans (1726). Recessive lethal mutations were induced in Drosophila melanogaster that

were exposed to concentrations as low as 0.2 ppm for 11 hours (1727). A significant and dose-dependent increase in the frequency of chromosomal aberrations and sister chromatid exchanges was seen in Chinese hamster cells exposed to EDB (1728). EDB has induced sister chromatid exchanges in human lymphocytes in vitro (1729). In 2 human lymphoblastoid cell lines, it induced gene mutations at the HGPRT locus (1730) and in L5178Y mouse lymphoma cells, Caspary et al. (3103) observed mutations at the TK locus.

In vivo studies in animals and man have given negative or marginal results. No dominant lethal effects were seen by Epstein et al. (998) in mice given single ip doses of 18 or 90 mg/kg or oral doses of 50 or 100 mg/kg daily for 5 days. Teramoto et al. (3706) gavaged male rats (10 or 30 mg/kg/day) and male mice (100 or 150 mg/kg/day) for 5 days with EDB and looked for dominant lethals in all germ cell stages, but did not observe any significant increase over controls. Krishna et al. (1761) observed that single ip doses of 84 or 168 mg/kg produced sister chromatid exchanges in mouse bone marrow cells at a rate slightly higher than controls but that these increases were not dose related. In the same study, the lowest dose of EDB (42 mg/kg) was more effective in inducing chromosome aberrations in bone marrow cells than were the two higher doses used (84 or 168 mg/kg). Steenland et al. (1731, 1732) found that neither short- nor long-term exposures to EDB caused any chromosomal abnormalities in humans. Short-term exposures were for an average of 14 days with an 8-hour TWA of 60 ppb. Long-term exposures were for an average of 5 years with an 8 hour TWA of 88 ppb. A recent study by Ratcliffe et al. (3584) conducted on a cohort of 46 male workers employed at papaya fumigation facilities in Hawai'i concluded that the workers had statistically significant decreases in sperm counts per ejaculate and in percentages of viable and motile sperm. The average exposure of the cohort was 5 years and the breathing zone exposures averaged 88 ppb.

45.3.1.3 Teratogenicity, Embryotoxicity and Reproductive Effects

EDB induces testicular damage at low doses. There is also evidence that EDB may induce sperm abnormalities and sperm death. In the NTP bioassay conducted with F344 rats (1743), testicular atrophy was observed in 4% of the low-dose animals (10 ppm) and in 10.2% of the high-dose (40 ppm) animals. Many cases of atrophy in the high-dose group were associated with testicular tumors and may not reflect direct EDB toxicity. Testicular degeneration, however, was found in 20% of the low-dose and 36.7% of the high-dose animals.

Oral doses of 38 or 41 mg/kg/day caused testicular atrophy at rates of 29 and 36%, respectively, after 49 weeks of administration to Osborne-Mendel rats. $B6C3F_1$ mice exhibited a 21% rate of atrophy after 78 weeks of oral doses of 107 mg/kg/day (1606). Intraperitoneal doses of 10 mg/kg for 5 days produced transient sterility in Wistar rats which resulted from damage to spermatids. Normal fertility returned after 5 weeks (1740).

Rats and mice exposed to 0, 20, 38 or 80 ppm EDB, 23 hours per day on days 6 through 16 of gestation showed no evidence of teratogenic effects. There was some

evidence of embryotoxicity as measured by increased resorptions but this was not statistically significant. There was also a minor incidence of external, soft-tissue and skeletal anomalies but these occurred only at concentrations that affected maternal welfare (1742). The effects of paternal ethylene dibromide exposure on F_1 generation behavior (3208) and on neurotransmitter enzymes in the developing F_1 brains (3308) have been studied in rats. Male rats were exposed by ip injections to 1.25, 2.5, 5.0, or 10.0 mg/kg/day EDB for 5 days. Four and/or nine weeks after the last injection the males were bred with untreated females. Significant differences in the development of motor coordination and motor activity were observed in the F_1 offsprings of both the 4th and 9th week breeding periods. In the study of neurotransmitter enzymes, male rats were exposed ip to 1 mg/kg/day EDB for 5 days. Seven days after the last injection, the males were bred with untreated females. The activities of several neurotransmitter enzymes were altered in the brains of the young pups of the treated males. Most of these enzyme values were in the normal range by 90 days after birth. These biochemical changes may be associated with behavioral abnormalities observed in the pup's early development.

45.3.1.4 Other Toxicologic Effects

45.3.1.4.1 Short-term Toxicity

Animal studies have confirmed that EDB is acutely toxic to the liver and kidneys, but near-lethal doses are required to produce observable organ damage (1745). Generally, the margin between the dose which is tolerated for long-term exposure and that causing severe injury and death is small (12).

Rowe et al. (1759) reported single oral dose LD_{50} values for several species of animals. These range from 55 mg/kg in female rabbits to 420 mg/kg in female mice. Values of 146 and 117 mg/kg were reported for male and female rats, respectively.

These investigators also studied the effects of EDB on various animal species by single and repeated inhalation exposures. The maximum survival times of rats exposed to EDB vapors were as follows: 3000 ppm for 6 minutes, 400 ppm for 30 minutes and 200 ppm for 2 hours. In female rats, the no adverse effect levels were 800 ppm for 6 minutes, 100 ppm for 2.5 hours and 50 ppm for 7 hours. The pathological changes noted were congestion, edema, hemorrhages and inflammation of the lungs; cloudy swelling, fatty degeneration and necrosis of the liver, and interstitial congestion, edema and cloudy swelling of the tubular epithelium of the kidney. No adverse effects were reported in rats and guinea pigs exposed to vapor levels of 25 ppm, 7 hours per day for 13 exposures in 17 days (1759).

In an early study by Kochman (1760), cats and rabbits were exposed to vapor levels of approximately 100 ppm for 30 minutes per day. The survival period for cats was approximately 10 days. Autopsy showed that the body cavities contained a clear, yellow liquid. The lungs were judged to be partially nonfunctional and contained dark red discolorations. The spleen was slightly enlarged and the kidneys were swollen and yellow colored. Fatty degeneration of the liver and tubular degeneration

of the kidney were also noted. Rabbits survived from 4 to 22 days. Autopsy revealed hyperemia of the liver and kidneys, blood in the colon and an excessive amount of liquid in the small intestine.

Dermal contact lasting for 24 hours was survived by 14 of 15 rabbits at a dose of 210 mg/kg but resulted in 100% mortality after a dose of 1100 mg/kg. In all of the exposed animals, EDB produced moderate to severe erythema, edema, skin necrosis and marked CNS depression (1759). A dermal LD_{∞} of 300 mg/kg in rats has been reported (47).

Undiluted EDB caused pain and conjunctival irritation when applied to the eyes of rabbits. Slight but superficial necrosis was also observed but healing was prompt and complete (1759).

4 5.3.1.4.2 Chronic Toxicity

Long-term exposure to EDB affects the lung, liver and kidneys. Rowe et al. (1759) investigated the chronic toxicity of EDB in rats, rabbits, guinea pigs and monkeys. Exposures to vapor levels of 25 ppm for 156 seven-hour exposures in 220 days caused no adverse effects, but exposures to 50 ppm, 7 hours per day, 5 days per week for 70-90 days was not well tolerated by any test species. Guinea pigs were the most sensitive exhibiting increased lung, liver and kidney weights, depressed body weight gain, slight central fatty degeneration of the liver and slight degeneration of the renal tubular epithelium. Rabbits showed only small increases in liver and kidney weights. Monkeys appeared ill, nervous and unkempt. Liver weights were increased, and there was very slight central fatty degeneration of the liver. Rats exhibited increased liver and kidney weights, increased lung weights and decreased testis weights in males and decreased spleen weights in females. In a 13-week study, Reznik et al. (1764) found histopathological changes to be limited to the respiratory tract in rats and mice exposed to 75 ppm EDB vapor 6 hours daily, 5 days per week. Changes in the nasal cavity included loss of cilia, cytomegaly, focal hyperplasia and squamous metaplasia. Other effects seen in the NCI carcinogenicity bioassay were degenerative changes in the liver and adrenal cortex in high and low dose rats and testicular atrophy in male rats and mice (1606).

45.3.2 Human and Epidemiologic Studies

45.3.2.1 Short-term Toxicologic Effects

Acute oral or inhalation exposure to EDB causes vomiting, diarrhea, abdominal pain and in some cases delayed lung damage and CNS depression (1745). In the past, EDB was occasionally confused with the anesthetic ethyl bromide. NIOSH (1741) reported an early case in which EDB was accidentally used in this manner. The female patient, after being administered the contents of a 70 g bottle, experienced symptoms of dizziness, vomiting, diarrhea, difficult breathing, thirst, abdominal pain and uterine hemorrhaging. She died within 44 hours of receiving the EDB. Autopsy results revealed skin vessels filled with blood and body cavities which

contained clear, red liquid. There were signs of upper respiratory tract irritation with extensive surface hemorrhage. The heart, liver and kidneys were in the advanced stages of parenchymatous degeneration. Microscopic examination showed fatty degeneration of the liver cells and cardiac musculature.

One case of ingestion of EDB has been reported (1746). In this instance, a 43-year-old woman ingested 4.5 mL (140 mg/kg bw) EDB in capsule form. She began vomiting immediately and continued to do so periodically for the next 48 hours. Diarrhea began after 24 hours. There was both a darkening of the urine and a decrease in volume after 36 hours. The patient was hospitalized 48 hours after ingestion and was completely anuric at this time. She did not improve after supportive treatment and died 54 hours after ingestion. Autopsy revealed no excess fluid in body cavities and no gross cardiac abnormalities. Microscopic examination showed massive hepatic necrosis with red blood cells in the sinusoids and scattered areas of yellow pigment. The kidneys were intensely congested with local damage in the proximal tubular epithelium.

Acute occupational exposure of workers cleaning a storage tank led to 2 additional fatalities (1747). The first worker collapsed within 5 minutes of entering the tank and died 12 hours later. A supervisor attempting to rescue the first worker also collapsed inside the tank and died 64 hours later. Both workers experienced nausea, vomiting, diarrhea, acute renal and hepatic failure and metabolic acidosis. Two hours after the accident 7.5 cm of liquid was found at the bottom of the tank. Upon analysis, it was found to contain between 0.1 and 0.3% EDB and traces of dichloropropene and dichloropropane and high concentrations of nitrates and phosphates. EDB was the only airborne toxicant detected. Levels ranged from 15 to 41 ppm. Death was attributed to dermal exposure for a 20-60 minute period. The inhalation of EDB was not considered to be a significant factor in this case because the air levels that were measured in the tank would not produce toxic effects in animals. An alternative cause of these fatalities was thought to be clostridial infections since 2 species of pathogenic clostridia were isolated from lung tissue (1748). This hypothesis was disputed because of the time frame which elapsed before death and because the victims had no predisposing factors (1749).

Liquid EDB is highly irritating to human skin causing marked erythema and vesiculation (46). Pflesser (1750) conducted a series of experiments in which EDB was in contact with the skin for various periods of time. In the first experiment, 0.5 mL of EDB was rubbed into the forearm for 1 minute and washed with soap and water 30 minutes later. All subjects developed swelling, reddening and itching within 24 hours. These subsided within 2-3 days. In another experiment, the subjects applied 0.5 mL EDB with a swab and covered the area for 10 minutes. During this time, slight burning was noticed. The area was then cleansed with soap and water. During the next 24 hours, reddening and swelling developed but disappeared in 3-5 days. In a subsequent experiment, the same procedure was repeated and the site was covered for 30 minutes. During the exposure, subjects reported burning at the application site. Within 15-20 minutes after exposure, there was painful inflammation

of the skin, which included reddening, swelling and blistering. The damaged skin healed after 7-13 days of supportive treatment.

EDB vapor is irritating to the eyes and there have been no reports of corneal opacification (19).

45.3.2.2 Chronic Toxicologic Effects

There is no conclusive evidence that long-term exposure to EDB causes cancer or adverse reproductive effects to humans. To evaluate long-term effects in humans, epidemiologic studies of workers occupationally exposed to EDB have been reported but substantial deficiencies have limited the use of these data in risk analysis.

In 1980, Ott et al. (1756) reported a retrospective mortality study of 161 male workers who were exposed to EDB in 2 manufacturing facilities. All workers were reactor and still operators. Sixty-two were employed in plant A, which operated from the mid 1920's until 1976. Workers at this plant were exposed to vapor levels ranging from 1 to 70 ppm. Besides EDB, workers at this plant were reportedly exposed to 25 other substances including bromine, benzene, substituted phenols, vinyl bromide, carbon tetrachloride and other halogenated hydrocarbons. The remaining 99 workers were employed at plant B, which operated from 1942 to 1969. In addition to EDB, these workers were exposed to bromine, ethylene, chlorine and sulfur dioxide. Vapor levels at plant B were not reported. There were 9 deaths due to malignant neoplasms, but this included 2 deaths from lung cancer in workers also exposed to arsenic. Since arsenic is known to increase the risk of lung cancer, these workers were excluded from the analysis. At plant A, there were 5 deaths versus 2.2 expected while at plant B there were 2 deaths versus 3.6 expected. The results of this study are inconclusive due to the small sample size, lack of EDB exposure data at plant B and exposure to other halogenated solvents.

TerHaar (1757) reported that EDB exposure for periods ranging from 3 months to 10 years resulted in 1 death from kidney cancer in 53 employees. In evaluating the reproductive toxicity of EDB, exposures at less than 5 ppm had no adverse effect on sperm counts. A retrospective evaluation of workers' reproductive histories found no significant difference between the observed and expected number of live births among 297 wives of the workers.

NIOSH recently reported a reproductive study conducted in 46 men exposed to a mean vapor level of 88 ppb EDB for 5 years. Statistically significant adverse reproductive effects which were noted included decreased sperm count, decreased percentage of viable and motile sperm, and an increased proportion of sperm with morphologic abnormalities (1758, 3584).

45.3.3 Levels of Concern

The USEPA has proposed an MCLG of 0 and an MCL or 0.05 μg/L for ethylene dibromide in drinking water (3883).

The ACGIH (3005) have given EDB an A2 (suspected human carcinogen) classification, with a recommendation that exposure be avoided. OSHA (3539) currently permits exposure to an 8-hour time-weighted-average of 20 ppm EDB, with a not-to-be-exceeded ceiling limit of 30 ppm during an 8-hour work-shift except for a peak level of 50 ppm for a duration of five minutes. OSHA (1398) has proposed but not yet enacted to lower employee exposure limits of 0.1 ppm (8-hr TWA) with a ceiling limit of 0.5 ppm. IARC (1357) lists ethylene dibromide in Category 2A (inadequate evidence of carcinogenicity in humans; sufficient evidence of carcinogenicity in animals) in its weight-of-evidence for potential carcinogens.

45.3.4 Hazard Assessment

EDB is carcinogenic to mice and rats by oral administration, producing squamous-cell carcinomas of the forestomach in both species (1606). Inhalation of EDB vapors produced alveolar/bronchiolar carcinomas, hemangiosarcomas and numerous other tumors in rats and mice (1743, 1744). EDB also produced skin, lung and forestomach tumors in mice after dermal application (142). Evidence for carcinogenicity to humans is inadequate. IARC has categorized EDB as a group 2B carcinogen. Results of NTP bioassay indicate clear evidence of carcinogenicity. The USEPA (3977) has calculated a 10^{-4} cancer risk of 0.04μg/L for drinking water.

There is also sufficient evidence to indicate mutagenic activity in a wide variety of nonmammalian test systems and in cultures of mammalian cells (1108, 1726, 1728, 1730).

EDB does not appear to be teratogenic in either rats or mice but it does induce testicular degeneration in these species at levels as low as 10 ppm (1742, 1606, 1743). A recent NIOSH report suggests possible human reproductive disorders in men exposed to a mean EDB vapor level of 88 ppb for 5 years (1758).

EDB vapor is irritant to eyes and mucous membranes, and high vapor concentrations can result in CNS depression (1745). Acute exposures may cause lung, liver and kidney damage (1759, 1745).

Prolonged contact of the liquid with the skin may cause erythema, blistering and skin ulcers; reactions may be delayed by 24-48 hours (46, 1750). Deaths have occurred in humans after the inadvertent ingestion (4.5 mL) or inhalation of EDB (1746, 1747).

45.4 SAMPLING AND ANALYSIS CONSIDERATIONS

Determination of ethylene dibromide concentrations in soil and water requires collection of a representative field sample and laboratory analysis. Due to the volatility of ethylene dibromide, care is required to prevent losses during sampling collection and storage. Soil and water samples are collected in airtight containers

with no headspace; analysis should be completed within 14 days of sampling. However, recent studies (3430) show large losses of volatiles from soil handling. At the present, the best procedure is to collect the needed sample in an EPA VOA vial, seal with a foil-lined septum cap, and analyze the entire contents in the vial using a modified purge and trap apparatus. In addition to the targeted samples, quality control samples such as field blanks, duplicates, and spiked matrices should be included in the analytical program.

Ethylene dibromide is not included among the EPA-designated priority pollutants and an EPA-approved procedure for the analysis of ethylene dibromide is not available. However, EPA Methods 601, 624, 1624 (65), 8010, and 8240 (63) would be appropriate methods of choice for the analysis of ethylene dibromide in aqueous samples. An inert gas is bubbled through the aqueous sample in a purging chamber at ambient temperature, transferring the ethylene dibromide from the aqueous phase to the vapor phase and onto a sorbent trap. The trap is then heated and backflushed to desorb the ethylene dibromide and transfer it onto a gas chromatographic (GC) column. The GC column is programmed to separate the volatile organics; ethylene dibromide is then detected with a halide specific detector (Methods 601 and 8010) or a mass spectrometer (Methods 624, 1624, and 8240). For samples that contain high concentrations, direct injection may also be used. The generalized procedure for sample preparation for the analysis of volatile organics by purge and trap (Method 5030) (63) also recommends that samples be screened prior to the purge and trap step to prevent contamination of the system. The recommended screening techniques involve the analysis of a headspace sample by GC with photo-ionization or electrolytic conductivity detectors or the analysis of a solvent extract by GC with flame ionization or electrolytic conductivity detectors.

The EPA procedures recommended for ethylene dibromide analysis in soil and waste samples, Methods 8010 and 8240 (63), differ from the aqueous procedures primarily in the method by which the analyte is introduced into the GC. The recommended method for low level samples (<1 mg/kg) involves dispersing the soil or waste sample in water and purging in a heated purge and trap device. The trap is desorbed and analyzed as described above. Recently introduced wide bore capillary columns show promise for increasing the performance of the GC analysis (3402, 3184, 3443).

Ethylene dibromide detection limits for the various methods were not determined but would be in the range of 1-10 $\mu g/L$ for aqueous samples and 1-10 $\mu g/kg$ for non-aqueous samples.

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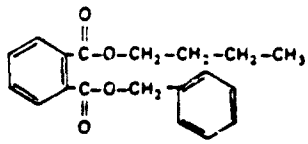
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COMMON SYNONYMS:	CAS REG.NO.: 85-68-7 FORMULA: $C_{19}H_{20}O_4$ NIOSH NO: TH9990000 STRUCTURE: 	AIR W/V CONVERSION FACTOR at 25°C (202) 12.8 mg/m³ ≈ 1 ppm; 0.078 ppm ≈ 1 mg/m³ MOLECULAR WEIGHT: 312.39
1,2-Benzenedicarboxylic acid, butyl phenylmethyl ester BBP Benzyl butyl phthalate Butyl benzyl phthalate Phthalic acid, butyl-benzyl ester		

REACTIVITY	Butyl benzyl phthalate is considered to be an ester for compatibility classification purposes. Such compounds generally evolve heat in reactions with non-oxidizing mineral acids or caustics. Reactions with oxidizing mineral acids, other strong oxidizers, or strong reducing agents may result in heat evolution and fire. Those with alkali or alkaline earth metals or nitrides may evolve heat and flammable gases, while those with hydrazines may produce heat and typically innocuous gases. Reactions with explosive materials may result in an explosion (51, 507, 511).

PHYSICO-CHEMICAL DATA	• Physical State: Liquid, oily (at 20°C)	(23)
	• Color: Clear	(23)
	• Odor: Slight	(23)
	• Odor Threshold: No data	
	• Density: 1.1130 to 1.1210 g/mL (at 25°C)	(23)
	• Freeze/Melt Point: -35.00°C	(59)
	• Boiling Point: 370.00°C	(59,507)
	• Flash Point: 199.00°C open cup	(23,60,506 507)
	• Flammable Limits: 0.26 (calc) to ? % by volume	(507)
	• Autoignition Temp.: No data	
	• Vapor Pressure: 8.60E-06 mm Hg, (estim) (at 20°C)	(507)
	• Satd. Conc. in Air: 1.4700E-01 mg/m³ (at 20°C)	(1219)
	• Solubility in Water: 2.90 mg/L (at 25°C)	(507)

PHYSICO-CHEMICAL DATA (Cont.)	• Viscosity: 47.000 cp (at 25°C) (507) • Surface Tension: 3.9900E+01 dyne/cm (at 25°C) (507) • Log (Octanol-Water Partition Coeff.): 4.77 (1657) • Soil Adsorp Coeff.: 2.84E+04 (1219) • Henry's Law Const.: 1.20E-06 atm · m^3/mol (at 20°C) (1219) • Bioconc. Factor: 6.63E+02 (bluegill) (399)
PERSISTENCE IN THE SOIL-WATER SYSTEM	BBP is expected to be relatively immobile due to strong soil sorption; however, complexation with organic substances may cause BBP to be mobilized and transported with groundwater. Volatilization is not expected to be significant. BBP is resistant to chemical degradation but is fairly easily biodegraded.
PATHWAYS OF EXPOSURE	The primary exposure pathway of concern from soil/ground-water systems is the migration of BBP to ground water drinking water supplies, although the situations where this will occur may be limited. Exposures through ingestion of foods contaminated with BBP may be important in some situations.
HEALTH HAZARD DATA	Signs and Symptoms of Short-term Human Exposure: No reports of adverse effects associated with human exposure were found. Acute Toxicity Studies: ORAL: LD_{50} 2330 mg/kg Rat (47) LD_{50} 20400 mg/kg Rat (3504) undiluted (see text) SKIN: LD_{50} 10000 mg/kg Rabbit (507) value is >10000

HEALTH HAZARD DATA	Long-Term Effects: Liver and kidney toxicity in rats Pregnancy/Neonate Data: Testicular degeneration in rats; no effect in mice or dogs Genotoxicity Data: Negative Carcinogenicity Classification: IARC- Group 3 (not classifiable as to its carcinogenicity to humans) NTP - Positive evidence in female rats, inconclusive in male rats, negative in mice EPA - Group C (possible human carcinogen)

HANDLING PRECAUTIONS (59,507)	Handle chemical only with adequate ventilation • There are no formal guidelines available for this chemical with respect to respirator use. It is recommended that exposure be kept below 5 mg/m^3. When this concentration is exceeded, a self-contained breathing apparatus or supplied air respirator may be required • Chemical goggles if there is probability of eye contact • Wearing of protective gloves is recommended.

ENVIRONMENTAL AND OCCUPATIONAL STANDARDS AND CRITERIA

AIR EXPOSURE LIMITS:

Standards
- OSHA TWA (8-hr): none established
- AFOSH PEL (8-hr TWA): none established

Criteria
- NIOSH IDLH (30-min): none established
- ACGIH TLV® (8-hr TWA): none established
- ACGIH STEL (15-min): none established

WATER EXPOSURE LIMITS:

Drinking Water Standards (3742)
0 µg/L (tentative)

EPA Health Advisories and Cancer Risk Levels
None established

ENVIRONMENTAL AND OCCUPATIONAL STANDARDS AND CRITERIA (Cont.)

WHO Drinking Water Guideline
No information available.

EPA Ambient Water Quality Criteria
- Human Health (355)
  - No criterion established due to insufficient data.

- Aquatic Life (355)
  - Freshwater species
    acute toxicity:
    no criterion, but lowest effect level occurs at 940 µg/L phthalate esters.

    chronic toxicity:
    no criterion, but lowest effect level occurs at 3 µg/L phthalate esters.

  - Saltwater species
    acute toxicity:
    no criterion, but lowest effect level occurs at 2944 µg/L phthalate esters.

    chronic toxicity:
    no criterion established due to insufficient data.

REFERENCE DOSES:
ORAL: 2.000E+02 µg/kg/day (374)

REGULATORY STATUS (as of 01-MAR-89)

Promulgated Regulations
- Federal Programs

  Clean Water Act (CWA)
  Butyl benzyl phthalate is listed as a toxic pollutant, subject to general pretreatment regulations for new and existing sources, and effluent standards and guidelines (351, 3763). Effluent limitations specific to this chemical have been set in the following point source categories: electroplating (3767), steam electric power generating (3802), metal finishing (3768), and metal molding and casting (892). Limitations vary depending on the type of plant and industry.

  Safe Drinking Water Act (SDWA)
  Phthalates are on the list of 83 contaminants required to be regulated under the SDWA of 1974 as amended in 1986 (3781). In states with an approved Underground Injection Control program, a permit is required for the injection of butyl benzyl phthalate-containing wastes designated as hazardous under RCRA (295).

Resource Conservation and Recovery Act (RCRA)
Butyl benzyl phthalate is listed as a hazardous waste constituent (3783). Wastestreams from the production of phthallic anhydride from naphthalene are listed as specific sources of phthallic acid-containing toxic hazardous waste (3774, 3765). Butyl benzyl phthalate is subject to land disposal restrictions when its concentration as a hazardous constituent of certain wastewaters exceeds designated levels (3785). Effective November 8, 1988, land disposal of certain untreated butyl benzyl phthalate-containing hazardous wastes is prohibited. These wastes must be treated according to Best Demonstrated Available Technology (BDAT) treatment standards before being disposed. Certain variances exist until May, 1990 for other hazardous wastes for which BDAT treatment standards have not been promulgated by EPA (3786). Butyl benzyl phthalate is included on EPA's ground-water monitoring list. EPA requires that all hazardous waste treatment, storage, and disposal facilities monitor their ground-water for chemicals on this list when suspected contamination is first detected and annually thereafter (3775).

Toxic Substances Control Act (TSCA)
Manufacturers, processors or distributors of butyl benzyl phthalate must report production, usage and disposal information to EPA. They, as well as others who possess health and safety studies on butyl benzyl phthalate, must submit them to EPA (334, 3789).

Comprehensive Environmental Response, Compensation and Liability Act (CERCLA)
Butyl benzyl phthalate is designated a hazardous substance under CERCLA. It has a reportable quantity (RQ) limit of 45.4 kg. Reportable quantities have also been issued for RCRA hazardous waste streams containing butyl benzyl phthalate but these depend upon the concentrations of the chemicals in the waste stream (3766). Under SARA Title III Section 313, manufacturers, processors, importers, and users of butyl benzyl phthalate must report annually to EPA and state officials their releases of this chemical to their environment (3787).

Federal Insecticide, Fungicide and Rodenticide Act (FIFRA)
Butyl benzyl phthalate is exempt from the requirement of a tolerance for residues in or on cotton seed when used as an inert plasticizer in the formulation of controlled release laminated dispensers of gossyplure. It is also exempt from a tolerance requirement for residues in or on artichokes when used as an inert plasticizer in multi-layered laminated controlled release dispensers of (Z)-11-hexadecenal (983).

Marine Protection Research and Sanctuaries Act (MPRSA)
Ocean dumping of organohalogen compounds as well as the dumping of known or suspected carcinogens, mutagens or teratogens is prohibited except when they are present as trace contaminants. Permit applicants are exempt from these regulations if they can demonstrate that such chemical constituents are non-toxic and non-bioaccumulative in the marine environment or are rapidly rendered harmless by physical, chemical or biological processes in the sea (309).

Hazardous Materials Transportation Act (HMTA)
The Department of Transportation has designated butyl benzyl phthalate as a hazardous material with a reportable quantity of 45.4 kg, subject to requirements for packaging, labeling and transportation (3180).

Food, Drug and Cosmetic Act (FDCA)
Butyl benzyl phthalate is approved for use as an indirect food additive as a component of adhesives (3209).

- State Water Programs

ALL STATES
All states have adopted EPA Ambient Water Quality Criteria and NPDWRs (see Water Exposure Limits section) as their promulgated state regulations, either by narrative reference or by relisting the specific numeric criteria. These states have promulgated additional or more stringent criteria:

KANSAS
Kansas has a quantification limit of 10 µg/L for ground-water (3213).

NEW YORK
New York has an MCL of 50 µg/L for butyl benzyl phthalate in drinking water, and a nonenforceable water quality guideline of 50 µg/L for surface and ground-waters (3501).

OKLAHOMA
Oklahoma has a water quality criterion of 0.150 mg/L for surface water (3534).

RHODE ISLAND
Rhode Island has an acute freshwater quality guideline of 85 µg/L and a chronic guideline of 1.9 µg/L for the protection of aquatic life in surface waters. These guidelines are enforceable under Rhode Island state law (3590).

SOUTH DAKOTA
South Dakota requires phthalates to be nondetectable, using designated test methods, in ground-water (3671).

Proposed Regulations

- Federal Programs

  Safe Drinking Water Act (SDWA)

  EPA will propose MCLs, MCLGs, and monitoring requirements for phthalates in March, 1990, with final promulgation scheduled for March, 1991 (3751).

- State Water Programs

  MOST STATES

  Most states are in the process of revising their water programs and proposing changes in their regulations which will follow EPA's changes when they become final. Contact with state officers is advised. Changes are projected for 1989-90 (3683).

  NONE

  No regulations are pending.

EEC Directives

Directive on Ground-Water (538)

Direct discharge into ground-water (i.e., without percolation through the ground or subsoil) of organophosphorous compounds, organohalogen compounds and substances which may form such compounds in the aquatic environment, substances which possess carcinogenic, mutagenic or teratogenic properties in or via the aquatic environment and mineral oils and hydrocarbons is prohibited. Appropriate measures deemed necessary to prevent indirect discharge into ground-water (i.e., via percolation through ground or subsoil) of these substances shall be taken by member countries.

EEC Directives -Proposed Resolution

Resolution on a Revised List of Second-Category Pollutants (545)

Butyl benzyl phthalate is one of the second-category pollutants to be studied by the Commission in the programme of action of the European Communities on Environment in order to reduce pollution and nuisances in the air and water. Risk to human health and the environment, limits of pollutant levels in the environment, and determination of quality standards to be applied will be assessed.

46.1 MAJOR USES

Butyl benzyl phthalate (BBP) is used exclusively as a plasticizer (202). Fifty percent goes into polyvinyl chloride-based flooring products; another important use is in polyvinyl acetate emulsions used as adhesives in the packaging industry (202). BBP is approved by the U.S. Food and Drug Administration for use in food contact articles (362). BBP is also used as a plasticizer with other polymers, including ethyl cellulose, acrylic resins, polyvinyl formal and polyvinyl butyral (202).

46.2 ENVIRONMENTAL FATE AND EXPOSURE PATHWAYS

46.2.1 Transport in Soil/Ground-water Systems

46.2.1.1 Overview

BBP may move through the soil/ground-water system when present at low concentrations (dissolved in water and sorbed on soil) or as a separate organic phase (resulting from a spill of significant quantities of the chemical). In general, transport pathways can be assessed with the use of an equilibrium partitioning model as shown in Table 46-1. These calculations predict the partitioning of low soil concentrations of BBP among soil particles, soil water, and soil air. The portions of BBP associated with the water and air phases of the soil are more mobile than the adsorbed portion.

The estimates (see Table 46-1) for the unsaturated topsoil model indicate that essentially all of the chemical (99.98%) would be sorbed on the soil; a relatively small amount (0.02%) of the chemical will be present in the soil-water phase and could thus migrate by bulk transport (e.g., the downward movement of infiltrating water), dispersion and diffusion. For the very small portion of BBP in the gaseous phase of the soil (1E-06%), diffusion through the soil-air pores up to the ground surface, and subsequent removal by wind, is possible.

In saturated, deep soils (containing no soil air and negligible soil organic carbon), a higher fraction of the BBP (0.8%) is likely to be present in the soil-water phase (Table 46-1) and transported with flowing ground water. However, most of the BBP is still expected to be adsorbed on soils, and ground waters underlying BBP-contaminated soils with low organic content may not be affected unless the BBP is mobilized by complexation with other species. It has been reported that phthalate esters readily interact with the fulvic acid in humic substances in water and soil. The interaction forms a fulvic acid-phthalate complex which is highly water soluble, allowing the otherwise insoluble phthalate esters to be mobilized and transported (766).

TABLE 46-1
EQUILIBRIUM PARTITIONING CALCULATIONS FOR BUTYL BENZYL PHTHALATE IN MODEL ENVIRONMENTS[a]

Soil Environment	Estimated Percent of Total Mass of Chemical in Each Compartment		
	Soil	Soil-Water	Soil-Air
Unsaturated topsoil at 25°C[c]	99.98	0.02	10E-06
Saturated deep soil[d]	99.2	0.8	-

a) Calculations based on Mackay's equilibrium partitioning model (34, 35, 36); see Introduction in Volume 1 for description of model and environmental conditions chosen to represent an unsaturated topsoil and saturated deep soil. Calculated percentages should be considered as rough estimates and used only for general guidance.
b) Used estimated soil sorption coefficient: K_{oc} = 28,400 (Estimated by Arthur D. Little, Inc.)
c) Henry's law constant taken as 1.2E-06 atm · m³/mol at 25°C (Estimated by Arthur D. Little, Inc.)
d) Used sorption coefficient calculated as a function of K_{oc} assuming 0.1% organic carbon: $K_p = 0.001 \times K_{oc}$

46.2.1.2 Sorption on Soils

The mobility of BBP in the soil/ground-water environment (and its eventual migration into aquifers) is strongly affected by the extent of its sorption on soil particles. In general, sorption on soils is expected to:

- increase with increasing soil organic matter content (except that complexation with humic or fulvic acids may decrease the extent of sorption);
- increase slightly with decreasing temperatures;
- increase moderately with increasing salinity of the soil water (701); and
- decrease moderately with increasing dissolved organic matter content of the soil water.

Log K_{oc} values for BBP have been reported to range from 3.57 to 5.63 (657, 1656, 1657). Based upon log K_{oc} of 4.77 (1657), the soil sorption coefficient (K_{oc}) is estimated to be 28,400. This is a relatively high value, indicative of strong sorption to soils. Gledhill et al. (1657) determined partition coefficients (mg/g : mg/mL) for BBP sorption onto three soils with organic matter ranging from 1.2% to 3.4%; the

measured partition coefficients ranged from 68 to 350. As mentioned above, phthalate esters have been shown to complex with natural organic substances (e.g., fulvic acid) to form water soluble complexes (765, 766, 767). Thus, sorption in soil/ground-water systems may be significantly weaker than might otherwise be expected.

46.2.1.3 Volatilization from Soils

Transport of BBP vapors through the air-filled pores of unsaturated soils is not expected to be an important transport mechanism except for near-surface dry soils. The very low value of Henry's law constant for BBP (1.2E-06 atm · m^3/mol at 25°C) implies that, when water is present, nearly all the BBP will be in the water or soil compartment (see Table 46-1). No significant volatilization was observed in an experiment with phthalate esters in activated sludge (1658). In contrast, there is evidence that phthalate esters are slowly volatilized from plastics into the air (10). However, since BBP is expected to be readily sorbed onto soils, volatilization is not expected to be a significant transport process in soil/ground-water systems.

46.2.2 Transformation Processes in Soil/Ground-water Systems

The persistence of BBP in soil/ground-water systems is not well documented. Photolysis and oxidation are not expected to be significant transformation processes in natural soils, and hydrolysis does not appear to be a major degradation pathway under normal environmental conditions. Wolfe et al. (658) examined the rate of hydrolysis for several phthalate esters, not including BBP, and found half-lives in water at pH 7 on the order of 3.2 to 2,000 years (10). Other investigators report half-lives ranging from 80 to 4,000 days at pH 8 and 30°C (1660). The hydrolysis of phthalate esters is catalyzed by both acids and bases (10). A 20°C drop in temperature (to a more typical ground-water temperature of 10°C) would increase the 30°C hydrolysis half-life by a factor of about 5.

Persistence studies indicate that biodegradation is the most important process for destruction of BBP in the environment (1657, 10, 524, 768). The data show that there are a number of microorganisms capable of using BBP as the sole source of carbon, and that ultimate degradation is possible. Biodegradation of BBP probably involves enzymic hydrolysis, and can depend on temperature, pH, oxygen content of environment, and other variables (10). Tabak et al. (55) have shown that BBP is easily degraded in active mixed cultures (and thus in sewage treatment plants), and have characterized BBP as undergoing "significant degradation [with] rapid adaptation."

Results of persistence studies for BBP are summarized in Table 46-2. There are no data available on BBP biodegradation in natural soil systems. Biodegradation of BBP proceeds rapidly in aerobic systems and more slowly under anaerobic conditions. Shelton et al. (1659) report that the initial steps in phthalate metabolism appear to be identical under aerobic and anaerobic conditions. In experiments with undiluted

TABLE 46-2

BIODEGRADATION OF BUTYL BENZYL PHTHALATE

	Degradation			
	Primary	Ultimate	Time (days)	$t_{1/2}$ (days)
• Activated sludge,				
Aerobic	93-99%[a]		1	
Aerobic	99%[b]		2	
Anaerobic		75%[c]		14
• Shake flask,				
acclimated	77%[b]	43%[b]	28	
• CO_2 evolution,				
aerobic	96%[a]	28		
• Gas production,				
anaerobic		<10%[a]	28	
• River water	100%[a]		9	2
• Lake water				
microcosm	95%[a]		7	<4
		51-65%[a]	28	

a) Reference 1657
b) Reference 678
c) Reference 1659

anaerobic digester sludge (1659), BBP was shown to be 75% degraded in two weeks; using sludge diluted to 10%, the degradation was slower (76 to 103% in 30 days). Lag times on the order of 1-2 weeks have been reported for BBP under both aerobic and anaerobic conditions; complete degradation may not occur within the retention times of some municipal sludge digesters (678, 1659).

In most soil/ground-water systems, the concentration of naturally occurring microorganisms capable of biodegrading chemicals such as BBP may be low and would drop off sharply with increasing depth. Thus, biodegradation in the soil/ground-water environment may be of minimal importance except, perhaps, in near-surface soils and in landfills with active microbiological populations.

46.2.3 Primary Routes of Exposure from Soil/Ground-water Systems

The above discussion of fate pathways suggests that BBP has a low volatility, is strongly sorbed to soil, and has a high potential for bioaccumulation. These fate characteristics suggest several potential exposure pathways.

Volatilization of BBP from disposal sites is not likely to represent an important exposure pathway under most conditions. Drinking water contamination resulting from

the migration of BBP with ground water may occur, particularly in deep or sandy soils. The potential for the formation of soluble complexes may make the possibility of drinking water contamination by BBP more likely than expected based on its properties. However, no data were found to indicate that BBP contamination of ground water is a common occurrence.

The movement of BBP in ground water, or its movement with soil particles, may result in discharges to surface waters. Consequently, ingestion exposures may occur through the use of surface waters as drinking water supplies, and dermal exposures may result from the recreational use of surface waters. In addition, BBP may be taken up by aquatic organisms and result in ingestion exposures for humans. The biodegradation of BBP may limit the extent to which these pathways are important.

46.2.4 Other Sources of Human Exposure

BBP is used as a plasticizer, particularly for polyvinyl chloride. Its primary use is in floor covering. As a result of its production and use, this compound is detected in surface waters and sediment in the U.S. An analysis of available data showed that 3% of the 1220 available data points had detectable concentrations of BBP. The median concentration in water was less than 10 mg/L, the most frequently stated detection limit. It was found in 6% of the 392 sediment stations with a median concentration of less than 500 mg/kg dry weight, and in 3% of 182 biota samples with a median concentration of less than 2.5 mg/kg (1417). These data suggest that ambient exposure to BBP is limited and at low levels.

The use of products containing BBP may result in exposure to the consumer. Releases of some phthalates from consumer products have been measured, however, no data were found for BBP.

46.3 HUMAN HEALTH CONSIDERATIONS

46.3.1 Animal Studies

46.3.1.1 Carcinogenicity

The National Toxicology Program conducted a carcinogenesis bioassay with BBP in B6C3F$_1$ mice and F344/N rats. Both species were fed diets containing either 6000 or 12,000 ppm BBP for 28 to 103 weeks. There was no increased incidence of any type of tumor among male or female mice at 103 weeks. The male rat study was discontinued after 28 weeks due to unexplained but compound-related internal hemorrhaging which resulted in a large number of deaths. Mononuclear cell leukemias occurred at a statistically significant incidence in high dose female rats (36%) when compared with the low dose (14%) and control groups (14%). The historical incidence at the laboratory for female F344/N rats for this type of leukemia is 19%. Under the conditions of the study, BBP was not carcinogenic for mice of

either sex, probably carcinogenic for female rats and inadequately tested in male F344 rats (1410).

Theiss et al. (1411) reported that groups of 20 Strain A male mice given intraperitoneal injections of up to 800 mg/kg BBP 3 times weekly for 8 weeks displayed no increased incidence of pulmonary adenomas compared with saline injected controls (0.10 to 0.25 lung tumors/mouse were found in treated animals vs. 0.19 in saline controls). In this case, the negative result cannot be taken as evidence of non-carcinogenicity because the length of the study was inadequate.

46.3.1.2 Genotoxicity

Mutagenicity tests conducted with BBP have given negative results. It has been tested with Salmonella typhimurium strains TA98, TA100, TA1535, and TA1537 with and without metabolic activation (1412), Saccharomyces cerevisiae D4, Escherichia coli, Bacillus subtilis and L5178Y mouse lymphoma cells (202) with negative results. Negative findings were also noted in mammalian cytogenetic studies using Chinese hamster ovary cells to detect chromosome aberrations and sister chromatid exchanges (1410).

46.3.1.3 Teratogenicity, Embryotoxicity and Reproductive Effects

BBP was shown to be lethal in the chick embryo system by Haberman et al. (1414). Nine-day chick embryos in ovo were injected with 0.1 mL of a 5% suspension of BBP in Hank's balanced salt solution into either the allantoic cavity or the chorioallantoic membrane (CAM). BBP injected into the CAM caused 68% mortality in the embryos compared with 27% in controls. Injection into the allantoic cavity caused 28% of the embryos to die in ovo compared with 18% in controls. Neonatal death rates at 21 days of age were not affected.

Bower et al. (1415) injected 0.05 ml of undiluted BBP into the yolk sac of fertilized chick eggs between the 65th and 72nd hour of development. Of the BBP-treated embryos, 48.8% died before hatching compared with 31.1, 53.4, and 44.8% in uninoculated, vegetable oil and sesame oil treated controls, respectively. There were no congenital malformations in any of the hatched chicks. The ED_{50} for chicken embryo observed by Korhonen et al. (3375) was 27 μmol/egg when fertile eggs were injected with BBP on day 3 of incubation. Increased malformations (small eye cups, malformed lids and cornea, and short lower beak) were found in the chicks exposed to 25 μmol/egg, but not in chicks exposed to 13 μmol/egg.

No evidence of fetotoxicity or teratogenicity was observed in the offspring in female rabbits treated with oral doses of 3 or 10 mg/kg BBP on days 6 through 18 of gestation (507). In rats, BBP appears to exert a direct toxic effect on the testis with secondary effects on other reproductive organs. In adult male Fischer 344 rats fed levels of 0.625, 1.25, 2.5 or 5.0% BBP in their diet for 14 days, the absolute weights of testis, epididymis, prostate and seminal vesicles were reduced in a dose-dependent manner at the 2.5 and 5% levels. These weight reductions were associated with

generalized histological atrophy of these tissues, with a clear relationship between dose and the severity of morphological changes in the testis, seminal vesicles, and prostate. Sperm granulomas were observed in one of the ten animals in both the 2.5 and 5.0% groups (1413). Dermal application of 4 mL/kg (4.45 g/kg) to the testes of rats was found to cause deviations in sperm mobility but did not induce damage to the testis (59).

46.3.1.4 Other Toxicologic Effects

46.3.1.4.1 Short-term Toxicity

The acute toxicity of BBP is low; oral LD_{50} values of 2330 and 4170 mg/kg are reported for the rat and mouse, respectively (47). A much higher oral LD_{50} for BBP of 20,400 mg/kg was reported by Hammond et al. (3264) when the undiluted material was administered. Some commonly used vehicles such as corn oil can alter the absorption and metabolism of the test compound (3264). The dermal LD_{50} value for rabbits is greater than 10,000 mg/kg (507).

In a 1952 study, both oral doses of 1.8 g/kg and ip doses of 4 g/kg caused rats to die after 4 to 8 days. Histopathological studies revealed toxic splenitis and degeneration of CNS tissue with congestive encephalopathy (1416).

In four-week oral toxicity studies with rats fed diets containing concentrations equivalent to 500, 1000, 1500, 2000, or 3000 mg BBP/kg body weight, decreased food consumption and depressed body weight gain were noted in the "high dose" groups. Weakness and loss of coordination were observed in animals receiving a dosage of 2000 or 3000 mg/kg (507).

Rats exposed to vapor concentrations of 0.36, 1.0, or 2.1 mg/L (≈332, 922, or 1936 mg/m^3), 6 hours per day, 5 days per week for 4 weeks had decreased body weight at the high dose levels. Atrophic spleens and reproductive organs were also noted in high dose males (507). In a another four-week inhalation study, no significant adverse effects were observed in rats exposed to 40, 150, or 500 mg/m^3. No dosing schedule was reported (507).

A 14-day feeding study with male Fischer 344 rats resulted in testicular degeneration at dietary levels of 50,000 or 100,000 mg/kg but not at 25,000 mg/kg (1410).

Mice fed up to 25,000 mg/kg for 14-90 days exhibited no gross or histological effects (1410).

Calley et al. (292) administered daily intraperitoneal injections of 500 mg/kg BBP (as a 3% acacia emulsion) to albino mice for 6 weeks. BBP had no effect on the final body weight or organ weights. Pathological changes included acute peritonitis, periportal hepatitis and extra medullary hematopoiesis in both the liver and spleen.

BBP did not cause either immediate nor delayed hypersensitivity reactions when evaluated in mice and guinea pigs (507).

46.3.1.4.2 Chronic Toxicity

Long-term administration of BBP causes liver and kidney effects in rats. Ninety-day studies at dietary concentrations of 2000, 5000, and 12,000 ppm daily caused increased liver weights in the high dose groups and increased kidney weights in both the high and low dose groups. Depressed weight gain and focal liver necrosis were noted in high dose animals. Pancreatic lesions were seen in the mid-dose animals (507).

Dogs which ingested diets containing 1, 2, or 5% BBP for 90 days reportedly exhibited no alterations in urinary or hematological parameters and no gross or histopathological effects (202).

Inhalation studies in rats exposed to BBP vapor concentrations of 0, 0.051, 0.218 or 0.799 mg/L (~3.7, 15.7, 57.4 ppm), 6 hours daily 5 days per week, for 13 weeks resulted in increased liver and kidney weights in the high exposure groups and increased kidney weights in mid-dose groups. The no-effect level was 0.051 mg/L (507).

46.3.2 Human and Epidemiologic Studies

46.3.2.1 Short-term Toxicologic Effects

Occupational exposure to BBP has not been reported to cause any significant adverse effects in humans. Dermal contact and inhalation are expected to be the primary routes of exposure.

A repeat insult patch test conducted on 200 human volunteers produced no positive reactions, leading to the conclusion that BBP is not a primary or cumulative skin irritant or sensitizing agent (507).

No specific exposure cases have been reported.

46.3.2.2 Chronic Toxicologic Effects

No data were found on the long-term effects of human exposure to BBP.

46.3.3 Levels of Concern

The USEPA (355) has not established an ambient quality criterion for the protection of human health due to insufficient data and neither OSHA (3539) nor the ACGIH (3005) have set a TWA exposure limit for BBP. An Oral Reference Dose of 200 μg/kg/day has been proposed by the USEPA (3742).

46.3.4 Hazard Assessment

BBP has a low order of acute toxicity in experimental animals by various routes of exposure. Long-term administration of BBP at dietary concentrations of 2000 ppm induced liver and kidney pathology in rats but not in dogs. Testicular degeneration has been reported in rats fed high levels (e.g., 25,000 ppm) of BBP in their diet (1410, 1413) but it is not seen in mice (1410) or dogs (202). Additional data are required to establish the implications of these findings to humans in view of the marked species differences and the high dose levels administered.

Oral administration of BBP in the diet of rats and mice resulted in no increased incidence of tumors in mice but did result in an increased incidence of mononuclear cell leukemias in high-dose female rats. The incidence of this type of tumor in the low-dose female group was comparable to that in controls. The compound was inadequately studied in male rats due to internal hemorrhaging which appeared to be compound-related, and resulted in a large number of early deaths (1410). IARC (3313) lists BBP in category 3 (no adequate data for carcinogenicity in humans; inadequaate evidence for carcinogenicity in animals) in its weight-of-evidence for potential carcinogens.

Mutagenicity studies in bacteria, yeast and mammalian cells are negative (202, 1410). Although lethal when injected directly into chick embryos, injection of BBP produced no congenital abnormalities and no adverse effects were observed in offspring of rabbits given 10 mg/kg BBP orally during gestation (507). Based on the lack of human data associated with exposure to BBP, no reliable assessment of hazard can be established for BBP without additional data. However, it should be noted, the adverse effects noted in animal studies all occur with very high exposure levels.

46.4 SAMPLING AND ANALYSIS CONSIDERATIONS

Determination of BBP concentrations in soil and water requires collection of a representative field sample and laboratory analysis. Care is required to prevent losses during sample collection and storage. Soil and water samples should be collected in glass containers; extraction of samples should be completed within 7 days of sampling and analysis completed within 40 days for aqueous samples and 30 days for non-aqueous samples. In addition to the targeted samples, quality control samples such as field blanks, duplicates, and spiked matrices may be specified in the recommended methods. Since phthalate esters are commonly found in many materials in the laboratory, method blanks must also be analyzed to demonstrate that the sample or extract has not been contaminated.

EPA-approved procedures for the analysis of BBP, one of the EPA priority pollutants, in aqueous samples include EPA Methods 606, 625, 1625 (65), 8060, and 8250 (63). Prior to analysis, samples are extracted with methylene chloride as a

solvent using a separatory funnel or a continuous liquid-liquid extractor. An aliquot of the concentrated sample extract (after solvent exchanging the methylene chloride for hexane in Methods 606 and 8060/ECD) is injected onto a gas chromatographic (GC) column using a solvent flush technique. The GC column is programmed to separate the semi-volatile organics; BBP is then detected with an electron capture detector (Methods 606 and 8060), a flame ionization detector (Methods 8060) or a mass spectrometer (Methods 625, 1625, and 8250).

The EPA procedures recommended for BBP analysis in soil and waste samples, Methods 8060 and 8250 (63), differ from the aqueous procedures primarily in the preparation of the sample extract. Solid samples are extracted using either soxhlet extraction or sonication methods. Neat and diluted organic liquids may be analyzed by direct injection.

Typical BBP detection limits that can be obtained in wastewaters and non-aqueous samples (wastes, soils, etc.) are shown below. The actual detection limit achieved in a given analysis will vary with instrument sensitivity and matrix effects.

Aqueous Detection Limit	Non-Aqueous Detection Limit
0.34 µg/L (Method 606)	1 µg/g (Method 8250)
2.5 µg/L (Method 625)	10 µg/g (Method 8060/FID)
10 µg/L (Method 1625)	0.2 µg/g (Method 8060/ECD)
0.15 µg/mL (Method 8060/FID)	1.7 µg/g (Method 8250)
3.4 µg/L (Method 8060/ECD)	
25 µg/L (Method 8250)	

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Note: The nonsequential numbers of the references reflect the order of references as they appear in the master bibliography.

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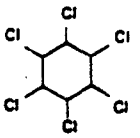
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COMMON SYNONYMS:	CAS REG.NO.: 58-89-9 FORMULA: $C_6H_6Cl_6$ NIOSH NO: GV4900000 STRUCTURE: 	AIR W/V CONVERSION FACTOR at 25°C (1098) 12.1 mg/m³ ≈ 1 ppm; 0.0826 ppm ≈ 1 mg/m³ MOLECULAR WEIGHT: 290.85
Cyclohexane 1,2,3,4,5,6-hexachloro-, gamma isomer Gamma-benzene hexachloride Gamma-BHC Gamma-HCH Lindane		

REACTIVITY	Lindane is considered to be a halogenated organic compound for compatibility classification purposes. Halogenated organic compounds typically generate heat in reactions with cyanides, mercaptans, and other organic sulfides. Those with non-oxidizing mineral acids, amines, and strong oxidizing agents typically evolve heat and toxic gases, while those with caustics or nitrides evolve heat and flammable gases. Reactions with oxidizing mineral acids may generate heat, toxic gases, and fire, while those with azo or diazo compounds or hydrazines may evolve heat and usually innocuous gases. Certain elemental metals and alloys as sheets, rods, drops, etc. may evolve heat and fire in reactions with these compounds, while alkali and alkaline earth elemental metals and metals as powders, vapors, or sponges may evolve heat and initiate an explosion. Heat and explosion are also possible results of reactions with organic peroxides, organic hydroperoxides, or strong reducing agents (511).

PHYSICO-CHEMICAL DATA	• Physical State: Solid, crystalline (at 20°C)	(54)
	• Color: Colorless-white	(0,54)
	• Odor: None	(38)
	• Odor Threshold: No data	
	• Density: 1.8500 g/mL (at 20°C)	(59)
	• Freeze/Melt Point: 112.00°C	(2)
	• Boiling Point: 323.40°C (decomposes)	(2)
	• Flash Point: Non-flammable	(60,504)
	• Flammable Limits: Non-flammable	(60,504)
	• Autoignition Temp.: Non-flammable	(60,504)

PHYSICO-CHEMICAL DATA (Cont.)	• Vapor Pressure: 9.40E-06 mm Hg (at 20°C)(59) • Satd. Conc. in Air: 1.4900E-01 mg/m³ (at 20°C) (1219) • Solubility in Water: 7.80E+00mg/L (at 25°C) (10,33) • Viscosity: No data • Surface Tension: No data • Log Octanol-Water Partition Coeff.): 3.72 (10,29) • Soil Adsorp. Coeff.: 2.50E+03 (estim) (611) • Henry's Law Const.: 4.80E-07 atm · m³/mol (at 20°C) (31) • Bioconc. Factor: 2.50E+02 (estim) (659)
PERSISTENCE IN THE SOIL-WATER SYSTEM	Lindane is expected to be moderately mobile and non-persistent in soil due to moderate sorption, volatilization, and relatively rapid biodegradation, particularly under anaerobic conditions. Risk of groundwater contamination is low except under conditions of heavy application or frequent rainfall/irrigation. Changes in soil moisture content are expected to be important in dissipation of lindane from soil.
PATHWAYS OF EXPOSURE	The primary pathway of concern from soil/ground-water systems is the migration of lindane to ground water drinking water supplies. Uptake by crops from soil or bioaccumulation by aquatic organisms or domestic animals may be important exposure pathways in some instances.

HEALTH HAZARD DATA	Signs and Symptoms of Short-term Human Exposure: (2, 15) Acute poisoning from ingestion or massive dermal exposure generally result in headache, nausea, vomiting, and respiratory problems. Lindane also stimulates the CNS causing hyperirritability, muscular incoordination, convulsions and coma. Acute Toxicity Studies: ORAL: LD_{50} 76 mg/kg — Rat (51) LD_{50} 25 mg/kg — Cat (3504) LD_{Lo} 111 mg/kg — Child (3504) LD_{50} 40 mg/kg — Dog (3504) SKIN: LD_{50} 500 mg/kg — Rat (51) Long-Term Effects: Liver and kidney damage Pregnancy/Neonate Data: Possibly embryotoxic Genotoxicity Data: Limited evidence Carcinogenicity Classification: IARC - None assigned (limited evidence in animals) NTP - Negative EPA - Group C (possible human carcinogen)
HANDLING PRECAUTIONS (54)	Handle chemical only with adequate ventilation • Vapor concentrations of <5 mg/m³: any chemical cartridge respirator with organic vapor cartridge and dust and mist filters or any supplied-air respirator or self-contained breathing apparatus • 5-25 mg/m³: any chemical cartridge respirator with organic vapor cartridges, full facepiece and dust and mist filter or any gas mask with organic vapor canister with dust and mist filter or any supplied air respirator with full facepiece or any self-contained breathing apparatus with full facepiece • 25-500 mg/m³: any powered air-purifying respirator with organic vapor cartridges and high-efficiency particulate filters or any Type C supplied-air respirator operated in pressure-demand or other positive pressure or continuous flow modes • Chemical goggles if there is a probability of eye contact • Protective clothing to prevent skin contact.

ENVIRONMENTAL AND OCCUPATIONAL STANDARDS AND CRITERIA

AIR EXPOSURE LIMITS:

Standards
- OSHA TWA (8-hr): 0.5 mg/m³ (skin)
- AFOSH PEL (8-hr TWA): 0.5 mg/m³ (skin); STEL (15-min): 1.5 mg/m³

Criteria
- NIOSH IDLH (30-min): 1000 mg/m³
- NIOSH REL: None established
- ACGIH TLV® (8-hr TWA): 0.5 mg/m³ (skin)
- ACGIH STEL (15-min): None established

WATER EXPOSURE LIMITS:

Drinking Water Standards (3883)
MCL (interim): 4 μg/L
MCLG: 0.2 μg/L (proposed)
MCL: 0.2 μg/L (proposed)

EPA Health Advisories and Cancer Risk Levels (3977)
The EPA has developed the following Health Advisories which provide specific advice on the levels of contaminants in drinking water at which adverse health effects would not be anticipated.

- 1-day (child): 1000 μg/L
- 10-day (child): 1000 μg/L
- longer-term (child): 30 μg/L
- longer-term (adult): 100 μg/L
- lifetime (adult): 0.2 μg/L
- 1E-04 cancer risk level: 0.3 μg/L

WHO Drinking Guideline (666)
A health-based guideline for drinking water of 3 μg/L is recommended for lindane. A daily per capita consumption of two liters of water was assumed.

EPA Ambient Water Quality Criteria
- Human Health (355)
  - Based on ingestion of contaminated water and aquatic organisms, (1E-05, 1E-06, 1E-07 cancer risk), 186 ng/L, 18.6 ng/L, 1.86 ng/L.
  - Based on ingestion of contaminated aquatic organism only, (1E-05, 1E-06, 1E-07 cancer risk), 625 ng/L, 62.5 ng/L, 6.25 ng/L.

ENVIRONMENTAL AND OCCUPATIONAL STANDARDS AND CRITERIA (Cont.)

- Aquatic Life (355)
  - Freshwater species
    The criterion to protect freshwater aquatic life as derived using the guidelines is 0.080 µg/L as a 24-hour average and the concentration should not exceed 2.0 µg/L at any time.

  - Saltwater species
    For saltwater aquatic life, the concentration of lindane should not exceed 0.16 µg/L at any time.

REFERENCE DOSES:
ORAL: 3.000E-01 µg/kg/day (3744)

REGULATORY STATUS (as of 01-MAR-89)

Promulgated Regulations
- Federal Programs

  Clean Water Act (CWA)
  Lindane is designated a hazardous substance. It has a reportable quantity (RQ) of 0.454 kg (347, 3764). It is also listed as a toxic pollutant, subject to pretreatment regulations for new and existing sources, and to effluent standards and guidelines (3763). Effluent limitations specific to this chemical have been set in the following point source categories: electroplating (3767), steam electric power generating (3802), metal finishing (3768), and pesticide chemicals (891). Limitations in the pesticide chemicals manufacturing category are set at 0.010 kg/1000 kg organic pesticide chemicals maximum for any one day (891). Limitations in other categories vary depending on the type of plant and industry.

  Safe Drinking Water Act (SDWA)
  Lindane is on the list of 83 contaminants required to be regulated under the SDWA of 1974 as amended in 1986 (3781). Under the National Primary Drinking Water Regulations, the maximum contaminant level (MCL) for lindane is 0.004 mg/L. This MCL applies to community water systems which serve a population of 10,000 people or more and which add a disinfectant as part of their treatment process (3801). In states with an approved Underground Injection Control program, a permit is required for the injection of lindane-containing wastes designated as hazardous under RCRA (295).

Resource Conservation and Recovery Act (RCRA)
Lindane is identified as a hazardous waste (U129) and listed as a hazardous waste constituent (3783, 3784). A non-specific source of lindane-containing waste is chlorinated aliphatic hydrocarbon production (325, 3765). Solid wastes are listed as hazardous when the TCLP extract concentration is equal to or greater than 0.4 mg/L lindane because they then exhibit the characteristic defined as EP toxicity (988). For ground-water protection, the maximum concentration of lindane-containing hazardous waste allowed in ground-water is 0.004 mg/L (989). Effective July 8, 1987, the land disposal of untreated hazardous wastes containing halogenated organic compounds in total concentrations greater than or equal to 1000 mg/kg is prohibited. Effective August 8, 1988, the underground injection into deep wells of these wastes is prohibited. Certain variances exist until May, 1990 for land and injection well disposal of some wastewaters and nonwastewaters for which Best Demonstrated Available Technology (BDAT) treatment standards have not been promulgated by EPA (3786). EPA requires that non-liquid hazardous wastes containing halogenated organic compounds (HOCs) in total concentrations greater than or equal to 1000 mg/kg or liquid hazardous wastes containing HOCs in total concentrations greater than or equal to 1% HOCs must be incinerated in accordance with the requirements of 40CFR264.343 or 265.343 (3782).

Comprehensive Environmental Response Compensation and Liability Act (CERCLA)
Lindane is designated a hazardous substance under CERCLA. It has a reportable quantity (RQ) limit of 0.454 kg. Reportable quantities have also been issued for RCRA hazardous waste streams containing lindane but these depend upon the concentrations of the chemicals in the waste stream (3766). Lindane is designated an extremely hazardous substance under SARA Title III Section 302. Any facility at which lindane is present in excess of its threshold planning quantity of 1000 pounds must notify state and local emergency planning officials. If lindane is released from the facility in excess of its reportable quantity (RQ), local emergency planning officials must be notified (3766). Under SARA Title III Section 313, manufacturers, processors, importers, and users of lindane must report annually to EPA and state officials their releases of this chemical to the environment (3787).

Federal Insecticide, Fungicide and Rodenticide Act (FIFRA)
EPA has cancelled the indoor use of lindane smoke fumigation devices and the use of lindane dog dips for control of all pests except mites. Lindane is classified for restricted use in certain commercial applications. Specific label modifications are required as well as the submission of mutagenicity data (1335). Tolerances have been established for lindane residues in or on raw agricultural commodities. Levels range from 0.01 to 7 ppm (314). Pesticide registration standards for lindane have been issued by EPA (3798).

Marine Protection Research and Sanctuaries Act (MPRSA)
Ocean dumping of organohalogen compounds as well as the dumping of known or suspected carcinogens, mutagens or teratogens is prohibited except when they are present as trace contaminants. Permit applicants are exempt from these regulations if they can demonstrate that such chemical constituents are non-toxic and non-bioaccumulative in the marine environment or are rapidly rendered harmless by physical, chemical or biological processes in the sea (309).

Occupational Safety and Health Act (OSHA)
Employee exposure to lindane shall not exceed an 8-hour time-weighted average (TWA) of 0.5 mg/m^3. An employee's skin exposure to lindane shall be prevented/reduced through the use of protective clothing and practices (3539).

Hazardous Materials Transportation Act (HMTA)
The Department of Transportation has designated lindane as a hazardous material with a reportable quantity of 0.454 kg, subject to requirements for packaging, labeling and transportation (3180).

Food, Drug and Cosmetic Act (FDCA)
The level for lindane in bottled drinking water is 0.004 mg/L. This level is identical to the maximum contaminant level (MCL) given under the Safe Drinking Water Act (365).

- State Water Programs

ALL STATES
All states have adopted EPA Ambient Water Quality Criteria and NPDWRs (see Water Exposure Limits section) as their promulgated state regulations, either by narrative reference or by relisting the specific numeric criteria. These states have promulgated additional or more stringent criteria:

CALIFORNIA
California has set a drinking water standard of 56 µg/L for Municipal Regions 1 and 5, and 4 µg/L (same as federal) for Municipal Regions 3, 4, 7 and 9 and Ocean Plan 1 (3097).

DISTRICT OF COLUMBIA
The District of Columbia has a water quality standard of 0.01 µg/L for surface waters classed for public water supply (3828).

FLORIDA
Florida requires that the level of lindane in Classes I and III fresh surface waters not exceed 0.01 µg/L, and not exceed 0.004 µg/L in Classes II and III marine surface waters (3220).

GEORGIA
Georgia has a water quality criterion of 0.08 µg/L for surface waters (3240).

MISSOURI
Missouri has a water quality criterion of 0.0022 µg/L for drinking water supply waters, and 0.062 µg/L for the protection of aquatic life in surface waters (3457).

NEW YORK
New York has set an MCL of 5 µg/L for all hexachlorocyclohexanes in drinking water (3501). New York has an ambient water quality standard for the protection of aquatic life of 0.01 µg/L for the sum of all hexachlorocyclohexane isomers in fresh surface waters classed A, A-S, AA, AA-S, B and C, and 0.004 µg/L for marine surface waters classed SA, SB and SC. In addition, New York has established a nonenforceable surface water quality guideline of 0.02 µg/L for human health, and requires that lindane be nondetectable in ground-water (3501, 3500).

NORTH CAROLINA
North Carolina has a water quality criterion of 0.01 µg/L for fresh surface waters (3681).

OHIO
Ohio sets a maximum concentration level of 0.019 µg/L for lindane in public water supplies (3533).

OKLAHOMA
Oklahoma requires that the instream concentration of lindane not exceed 2 µg/L for surface waters designated for fish and wildlife propagation (3534).

PENNSYLVANIA
Pennsylvania has a human health criterion (cancer risk level) of 0.02 µg/L for surface waters (3561).

VERMONT
Vermont has a preventive action limit of 0.02 µg/L and an enforcement standard of 0.2 µg/L for ground-water (3682).

VIRGINIA
Virginia sets a water quality criterion of 0.01 µg/L for ground-water (3135).

WISCONSIN
Wisconsin has a preventive action limit of 0.002 µg/L and an enforcement standard of 0.02 µg/L for lindane in ground-water (3840).

Proposed Regulations

- Federal Programs

  Safe Drinking Water Act (SDWA)

  EPA has proposed a maximum contaminant level goal(MCLG) of 0.2 µg/L for lindane as part of the National Primary Drinking Water Regulations (3772). EPA will repropose this MCLG and propose an MCL of 0.2 µg/L in May, 1989, with final action scheduled for May, 1990 (3759).

  Resource Conservation and Recovery Act (RCRA)

  EPA has proposed that solid wastes be listed as hazardous in that they exhibit the characteristic defined as EP toxicity when the TCLP extract concentration is equal to or greater than 0.06 mg/L lindane. Final promulgation of this Toxicity Characteristic Rule is expected in June, 1989 (1565).

- State Water Programs

  MOST STATES

  Most states are in the process of revising their water programs and proposing changes in their regulations which will follow EPA's changes when they become final. Contact with state officers is advised. Changes are projected for 1989-90 (3683).

  MINNESOTA

  Minnesota has proposed a Recommended Allowable Limit (RAL) of 0.3 µg/L for lindane in drinking water (3451). Minnesota has also proposed Sensitive Acute Limits (SAL) of 2 µg/L for cold surface waters and 10 µg/L for other designated surface waters, and chronic criteria of 0.3 µg/L for designated ground-waters and 0.04 µg/L for designated surface waters. These criteria are for the protection of human health (3452).

  NEW JERSEY

  New Jersey has proposed a water quality criterion of 0.004 µg/L lindane for the protection of aquatic life for all surface waters classed SE and SC (3496).

EEC Directives

Directive on Drinking Water (533)

The mandatory values for total pesticides in surface water treatment categories A1, A2 and A3 used or intended for abstraction of drinking water are 0.001, 0.00252 and 0.005 mg/L, respectively. There are no guideline values.

Directive Relating to the Quality of Water for Human Consumption (540)

The maximum admissible concentration for lindane is 0.1 µg/L. The total maximum allowable concentration for pesticides and related products is 0.5 µg/L.

Directive on Classification, Packaging and Labeling of Pesticides (786)
Lindane is listed as a Class I/c substance and is subject to packaging and labeling regulations.

Directive on the Classification, Packaging and Labeling of Dangerous Substances (787)
Lindane is classified as a toxic substance and is subject to packaging and labeling regulations.

Directive on Plant Protection Products (1333)
Plant protection products containing hexachlorocyclohexane with less than 99% of the gamma isomer may be neither placed on the market nor used. If it appears necessary, because of an unforeseeable danger threatening plant production which cannot be controlled by other means, such products may be permitted to be marketed and/or used for a maximum period of 120 days.

Directive on Ground-Water (538)
Direct discharge into ground-water (i.e., without percolation through the ground or subsoil) of organophosphorous compounds, organohalogen compounds and substances which may form such compounds in the aquatic environment, substances which possess carcinogenic, mutagenic or teratogenic properties in or via the aquatic environment and mineral oils and hydrocarbons is prohibited. Appropriate measures deemed necessary to prevent indirect discharge into ground-water (i.e., via percolation through ground or subsoil) of these substances shall be taken by member countries.

Directive on Bathing Water Quality (534)
When inspection of a bathing area shows that heavy metals, pesticides or cyanides may be present, concentrations should be checked by competent authorities.

Directive on the Quality Required of Shellfish Waters (537)
The mandatory specifications for organohalogenated substances state that the concentration of each substance in the shellfish water or in shellfish flesh must not reach or exceed a level which has harmful effects on the shellfish and larvae. The guideline specifications for organohalogenated substances state that the concentration of each substance in shellfish flesh must be so limited that it contributes to the high quality of shellfish product.

Directive on the Discharge of Dangerous Substances (535)
Organchalogens, organophosphates, petroleum hydrocarbons, carcinogens or substances which have a deleterious effect on the taste and/or odor of human food derived from aquatic environments cannot be discharged into inland surface waters, territorial waters or internal coastal waters without prior authorization from member countries which issue emission standards. A system of zero- emission applies to discharge of these substances into ground-water.

Directive on Marketing and Use of Dangerous Substances (541)
Lindane may not be used in ornamental objects intended to produce light or color effects by means of different phases

Directive on Hexachlorocyclohexane (1332)
The monthly limit values applicable to the total quantity of hexachlorocyclohexane (HCH) present in all water discharges coming from industrial plant sites are as follows: (1) In plants used for HCH production - 3 mg/L; (2) In plants used for lindane extraction - 8 mg/L; (3) In plants used for HCH production and the extraction of lindane - 6 mg/L. The total HCH concentration in inland surface waters affected by discharges and in estuary and territorial sea waters must not exceed 100 and 20 ng/L, respectively. In the case of water used for the abstraction of drinking water, the HCH content must conform to the requirements of the Directive on Drinking Water.

Directive on the Approximation of the Laws, Regulations and Administrative Provisions Relating to the Classification, Packaging and Labeling of Dangerous Preparations. (3991)

The labels on packages containing preparations classified as very toxic, toxic or corrosive must bear the safety advise S1/S2 and 346 in addition to the specific safety advice. If it is physically impossible to give such information, the package must be accompanied by precise and easily understood instructions.

EEC Directives - Proposed
Proposal for a Council Directive on the Dumping of Waste at Sea (1793)
EEC has proposed that the dumping of pesticides at sea be forbidden without prior issue of a special permit. Dumping areas shall be designated in the permit.

Resolution on a Revised List of Second-Category Pollutants (545)
Lindane is one of the second-category pollutants to be studied by the Commission in the programme of action of the European Communities on Environment in order to reduce pollution and nuisances in the air and water. Risk to human health and the environment, limits of pollutant levels in the environment, and determination of quality standards to be applied will be assessed.

EEC Directive - Regulation
Council Regulation Concerning Export From and Import Into the Community of Certain Dangerous Chemicals
EEC has required that any third country export of hexachlorocyclohexane (containing less than 99% of the gamma isomer) on its own or in preparations must be reported by the exporter to a designated authority in the state of export and the state of import. The product must be packaged and labeled in accordance with the Directive on Classification, Packaging and Labeling of Dangerous Substances. The designated authority should forward to the Commission all notification and relevant information as indicated in Article 7 of this regulation.

47.1 MAJOR USES

Lindane is the 99.5% pure gamma isomer of 1,2,3,4,5,6-hexachlorocyclohexane. It is used as an insecticide on cotton and other foliar plants, for soil and seed treatment of fruit and vegetable crops, and for the control of termites and other DDT-resistant insects (12). Lindane is also used as a therapeutic agent in veterinary and human medicine, i.e., for the ectoparasitic control of livestock, pets, and domestic animals; the 1% cream, lotion and shampoo are highly effective in combating human scabies and lice (12, 25). Registration of some lindane products, including its use in continuous vaporizers, on some agricultural crops, on dairy cattle and in dairy barns and milk rooms have been cancelled (17).

Lindane replaced hexachlorocyclohexane (a mixture of alpha, beta, delta and gamma isomers) for various insecticidal applications when it was discovered that almost all of the insecticidal activity resided in the gamma isomer, i.e., lindane. Hexachlorocyclohexane (also called benzene hexachloride or BHC) is no longer produced in the U.S. (17).

47.2 ENVIRONMENTAL FATE AND EXPOSURE PATHWAYS

47.2.1 Transport in Soil/Ground-water Systems

47.2.1.1 Overview

Lindane is expected to be relatively immobile in the soil/ground-water system when present at low dissolved concentrations. Lindane is a solid at ambient temperature (melting point is 112°C) and is generally dissolved in a solvent prior to application. Bulk quantities of the solution (e.g., from a spill, heavy spray application, or improper disposal of excess formulations) could be transported through the unsaturated zone. Most studies, however, have shown that proper application of lindane to soil surfaces does not result in rapid transport through the soil. Furthermore, as discussed later in this section, lindane has been shown to be susceptible to degradation in the soil/ground-water system.

In general, transport pathways can be assessed by using an equilibrium partitioning model, as shown in Table 47-1. These calculations predict the partitioning of low soil concentrations of lindane among soil particles, soil water and soil air. Portions of lindane associated with the water and air phases of the soil have higher mobility than the adsorbed portion. Estimates for the unsaturated topsoil model indicate that almost all (99.8%) of the lindane is expected to be associated with the stationary phase. Less than 1% is expected to partition to the soil-water phase; therefore, only a small portion would be available to migrate by bulk transport (e.g., the downward movement of infiltrating water), dispersion and diffusion. An insignificant portion of lindane is expected in the gaseous phase of the soil; diffusion of vapors through the

TABLE 47-1
EQUILIBRIUM PARTITIONING CALCULATIONS FOR LINDANE IN MODEL ENVIRONMENTS[a]

Soil Environment	Estimated Percent of Total Mass of Chemical in Each Compartment		
	Soil	Soil-Water	Soil-Air
Unsaturated topsoil at 25°C[b,c]	99.8	0.2	1E-05
Saturated deep soil[d]	91.4	8.6	-

a) Calculations based on Mackay's equilibrium partitioning model (34, 35, 36); see Introduction in Volume 1 for description of model and environmental conditions chosen to represent an unsaturated topsoil and saturated deep soil. Calculated percentages should be considered as rough estimates and used only for general guidance.
b) Utilized estimated soil sorption coefficient (611): K_{oc} = 2500.
c) Henry's law constant taken as 4.8E-07 atm · m^3/mol at 25°C. (31)
d) Used sorption coefficient K_{oc} = 0.001 K_{oc}.

soil-air pores up to the ground surface is not expected to be important (other data shown below indicate that entrainment with evaporating water may occur). In saturated, deep soils (containing no soil air and negligible soil organic carbon), a higher percentage of the lindane (8.6%) is predicted to be present in the soil-water phase (Table 47-1) and available for transport with flowing ground water. Sorption onto deep soils, however, is still expected to be significant.

Due to lindane's extensive use as an agricultural insecticide, several groups have studied its persistence in soil. Volatilization and biodegradation have been reported to be potentially important processes, while the leaching potential of lindane is expected to be relatively low compared to other commonly used chlorinated pesticides (1210). Bomberger et al. (1209) modeled the leachability of lindane in a soil system having 1% organic carbon, 50% porosity and 30% soil field capacity. After application of 305 cm water lindane migrated only 19 cm into the soil; the water front was estimated to be 1017 cm deep. In general, ground waters underlying lindane-contaminated soils are not expected to be highly vulnerable. However, in climates where precipitation greatly exceeds evaporation, lindane could be leached deep into the soil and represent a threat to ground water.

Comparative studies of the retention times of various chlorinated hydrocarbon pesticides in soil indicate that lindane disappears from soil relatively rapidly. In an

experimental study using two soils with organic content of 13% and 1%, the amounts of lindane found to persist after 128 days were 57% and 33%, respectively (1521). Another study (1530) reported lindane persistence in soil under very dry conditions with little or no runoff and under humid conditions with heavy rain. The observed half-lives for dry and humid soils were 50 days and 2 days, respectively; the corresponding periods for 99% disappearance were 500 days and 40 days. Maximum removal due to runoff was reported to be 0.03%.

A major review of lindane in soil presented the results of several investigators which indicated that lindane residues diminished 40-80% per year (1499). Other studies reported by the same author showed that 50% of surface-applied lindane disappeared within 4-6 weeks and 90% disappeared in 30-40 weeks. After being worked into the soil, however, it took 15-20 weeks for the disappearance of 50% of the lindane, and 2-3 years for disappearance of 90%. Additional data indicated only 0.2% of lindane applied at the rate of 10 kg/hectare was found in the soil 5 years after application. Under tropical conditions, lindane residues were reported to virtually disappear within 30 days.

Several studies (1501, 1502, 1503, 1504) have examined the persistence of lindane in soils used to grow crops. Under tropical conditions, reduction of lindane was generally reported to range from 70 to 90% over 2-3 months; one study reported reduction of 97.5% in 100 days. Reported uptake of lindane by the agricultural crops was minimal.

47.2.1.2 Sorption on Soils

There are several available studies addressing the adsorption and leachability of lindane on soils (1505, 1506, 1507). Values of the equilibrium soil sorption constant, K_{oc}, for lindane are in the range of 2500 (611) to 3800 (33). Sorption onto soils with organic content >0.1% is expected to occur, but not to the extent that leaching is completely prevented.

As with all neutral organic chemicals, the extent of sorption is proportional to the soil organic content. Sharom et al. (1505) reported Freundlich sorption constants for lindane adsorbed on four different soils; these are shown in Table 47-2. Experimental leaching studies performed by the same authors indicated moderate mobility for adsorbed lindane; 92.6% of the lindane sorbed to sand and 34.2% of that sorbed to organic soil was leached after ten successive 200 mL water rinses.

Chiou et al. (1508) examined the relative importance of soil organic matter and soil minerals in the sorption of lindane. They report that, in hydrated soils or aqueous systems, partitioning of lindane from water into the organic matter is the primary process of soil uptake and adsorption by soil minerals is relatively insignificant. However, in dehydrated soils, adsorption to soil minerals may be significant: the effectiveness of this adsorption is related to the ability of lindane to compete with the organic solvent for the polar mineral surfaces. Uptake of lindane applied to dry soils in nonpolar solvent, therefore, may be effected mainly through mineral

TABLE 47-2
FREUNDLICH SORPTION CONSTANTS FOR LINDANE

	1/n	K	Organic Content	Reference
Organic soil	0.98	899	75%	1505
Big Creek Sediment	0.96	24	2.8%	1505
Beverly Sandy Load	0.97	16	2.5%	1505
Plainfield Sand	0.99	8	0.7%	1505
Montmorillonite Clay/Water			-	
Sorption	0.662	1260		1515
Desorption	0.662	1260		1515
Sediment/Water			1.34%	
Sorption	0.926	350		1515
Desorption	1.96	4		1515
Sediment/Water			1.33%	
Sorption	1.265	60		1515
Desorption	0.529	11200		1515
Sediment/Water			0.55%	
Sorption	0.657	2200		1515
Desorption	1.72	4		1515

adsorption. Due to the strong ability of water to compete for polar surfaces, the application of water to the soils may cause desorption of lindane from the mineral sites, making it available for transport or re-adsorption to the organic matter.

Several authors (1506, 1507, 1509) examined the effects of temperature, period of contact, and pesticide concentration on adsorption and leachability of lindane in soils. Leaching of lindane from sandy clay loam (2.6% organic content) was relatively slow at all concentrations (1.6 μg/g soil-43.2 μg/g soil); at the lowest concentration, leaching was not detected until 200 days after application (1506). In general, leachability increased with lindane concentration. The data also suggest the downward movement of lindane through the soil; surface adsorption after leaching was minimal at all concentrations while adsorption at 16 cm was much higher.

Adsorption of lindane has been reported to occur rapidly after application (1507, 1509). In one experiment, lindane sorption onto a sand aquifer (1509) was reported to be rapid during the first four hours. with little additional sorption during the next 95 hours.

Retention of lindane on soil has also been shown to decrease progressively with increasing soil temperature (1507, 1509). El Beit et al. (1507) exhibited a drop from 40% adsorption at 2°C to 15% at 45°C. The observed decrease may be due to an increase in the leaching, evaporation, or degradation of lindane.

In summary, the available data suggest that sorption of lindane onto soils of moderate to high organic content will occur. However, evidence of leaching exists, particularly under conditions of high concentration, elevated temperature or frequent rainfall/irrigation.

47.2.1.3 Volatilization from Soils

Transport of lindane vapors through the air-filled pores of unsaturated soils is not expected to be a major transport pathway. Modeling results indicate that a very small fraction of the lindane loading will be present in the soil-air phase. However, due to its relatively high vapor pressure (1E-05 - 1E-04 mm Hg) and water solubility (10 mg/L), volatilization of lindane transported to the surface by evaporating water may be important.

Several authors (1510, 1511, 1512, 1513, 1514) have studied the effect of soil moisture content on the volatilization of lindane. In general, volatilization from soil is controlled by diffusion of the pesticide and by the mass flow of water to the surface. Evaporating water has been shown to enhance volatilization of lindane from soil due to the "wick effect," whereby the pesticide is carried to the surface in evaporating water, but not due to co-distillation with water vapor (1512).

The results of field experiments indicate that, with adequate moisture, pesticides applied to the surface of soil initially volatilize at rates proportional to the vapor density of the pure chemical. If the soil remains moist, volatilization appears to be controlled by diffusion; the time required for the volatilization rate to decline to half the initial rate is similar for most pesticides and ranges from 6-9 hours (1510). When moisture on soil surfaces decreases to an amount equal to one monomolecular layer, the effective vapor pressure of lindane and thus its volatilization is greatly reduced (above one to three molecular layers of absorbed water, soil moisture changes have less influence on volatilization). Laboratory and field studies have shown that relatively small amounts of moisture applied to the dry surface layer results in a marked increase in volatilization.

Glotfelty et al. (1511) presented volatilization data for lindane applied to the surface of a moist silt loam soil and a drier sandy loam. Initial rapid volatilization of lindane from the surface of the moist silt loam was observed: 50% lost in six hours, and 90% lost in six days. By contrast, losses from the surface of the sandy soil were much lower (12% lost after 50 hours), probably due to the lack of capillary wetting which created a dry soil surface; losses remained low until moisture was applied. Another study (1510) reported 78% volatilization from moist soil after 11 days.

Volatilization losses from environmental soils vary greatly with the extent of incorporation into the soil column and will generally be much lower than those reported for experimental surface soils. However, heavy application to vegetation or surface soils may yield extremely rapid volatilization and persistence within the affected area may be on the order of days rather than the longer times required for dissipation after incorporation into soil.

47.2.2 Transformation Processes in Soil/Ground-water Systems

Lindane has been reported to be susceptible to a number of degradation processes including hydrolysis, photolysis, and biodegradation. In persistence studies (1518), degradation (due to chemical and biological factors) was reported to increase with increases in pH, temperature, and ultraviolet irradiation.

The data addressing hydrolysis and photolysis in the soil/groundwater system are very limited. Lindane hydrolysis has been reported to be catalyzed by hydroxide and hydrogen ions; neutral hydrolysis was reported to be relatively unimportant. Experimental hydrolysis half-lives (first order) in natural water/sediment systems were determined to be 92 hours, 771 hours, and 648 hours for systems at pH 9.3, pH 7.3, and pH 7.8, respectively (1515). Other authors (1516, 1517) have reported aqueous hydrolysis half-lives of one to four years at pH 7 to pH 8. Direct photolysis of lindane in the environment is expected to be minimal due to its limited solar absorption (10). However, an adjusted mid-winter photolysis half-life for lindane in distilled water was reported to be 65 days; photolysis rate retardation was noted for natural water/sediment systems at pH 7.3 and pH 7.8, while enhancement was noted in natural water/sediment at pH 9.3, possibly due to alkaline hydrolysis side reactions promoting photodegradable intermediates (1515). Photolysis studies for lindane in aqueous solution containing soil fulvic acid as a photosensitizer yielded a half-life of 48 days (1519).

Studies on the biodegradation of lindane have been presented in a number of reports (10, 1499, 1501, 1520, 1521, 1522, 1209). The general conclusion is that, compared to other chlorinated pesticides, lindane is relatively biodegradable with half-lives ranging from several days to months when introduced into biologically active environments. Microbial degradation is expected to be greater under anaerobic conditions than under aerobic conditions. Major degradation products have been reported to be pentachlorocyclohexane (PCCH) and α-BHC; other degradation products include other BHC isomers, tetrachlorocyclohexanes, pentachlorobenzene, and tetrachlorobenzenes. These degradation products are expected to be more volatile than lindane.

Seventy-one of 147 microorganisms isolated from a sandy loam soil exhibited the ability to utilize lindane in solution as the sole carbon source after six weeks incubation (1523). Thirteen microorganisms were studied further; of these, three showed adaptation times of less than a day while four required five to seven days adaptation. In another study (1524), 53 aerobes and 18 anaerobes, out of 354 bacterial and fungal isolates, were shown to metabolize lindane. An anaerobic bacterial species in

pure culture was shown to degrade 3.7 ppm lindane to 0.02 ppm in 27 hours (1499). A 4000 ppm solution of lindane was shown to stimulate the growth of soil bacteria (1520).

Lindane added to a thick anaerobic sludge at 35°C was reported to be 95% transformed after several days; anaerobic processes were more effective than aerobic processes (1525). In an experiment using lake water/sediment, 15% and 90% degradation was observed after 87 days in aerobic and anaerobic environments, respectively (1526). In contrast, Mathur and Saha (1527) reported only 10% degradation after 42 days incubation of lindane in anaerobic flooded sandy soil.

Anaerobic degradation of lindane during composting has been shown to be rapid: 20-40% in 70 days during one experiment; 99% in 70 days during a second experiment (1522). In anaerobic soils, 50% of the applied lindane was transformed within 56 days (1528). When applied to an anaerobic mixed bacterial flora enriched from an arable soil, up to 90% of the lindane was degraded within four to five days (1529).

In most soil/ground-water systems, the natural concentration of microorganisms capable of biodegrading chemicals such as lindane is expected to be low and to drop off sharply with increasing depth. Thus, biodegradation in the soil environment may be slower than that reported in experimental data. The exception may be in areas with active microbiological populations, such as near landfills.

47.2.3 Primary Routes of Exposure from Soil/Ground-water Systems

The above discussion of fate pathways suggests that lindane has a low volatility; is moderately to strongly sorbed to soil, and has a moderate potential for bioaccumulation. These fate characteristics suggest several potential exposure pathways.

Volatilization of lindane from a disposal site is not likely to represent a major exposure pathway for workers or residents in the area. There is a potential for lindane to contaminate ground water, particularly in sandy soils. Mitre (83) reported that lindane has been found at 7 of the 546 National Priority List (NPL) sites. It was detected at 5 sites in ground water, 5 sites in surface water, and one site in air. However, contamination of ground-water drinking water supplies does not appear to be common or at high levels. National compliance data showed that no public ground water systems exceeded the MCL for lindane (0.004 mg/L) (992). In the Rural Water Survey, one out of 71 ground-water systems exceeded the minimum quantification limit (0.002 mg/L) for lindane. In the National Organics Reconnaissance Survey (NORS), two ground-water systems contained lindane, but at levels less than the minimum quantifiable limit (992). In some cases, either related to high use areas or to specific site conditions, lindane can be found more commonly in ground water. EPA (992) reported that a survey of ground-water supplies in one state showed that 58.3% of the samples contained lindane at levels greater than 0.01 µg/L.

The movement of lindane in ground water may result in discharges to surface water. As a result, ingestion exposures may occur, resulting from the use of surface water as a drinking water supply, and dermal exposures may occur resulting from the recreational use of surface waters. In addition, lindane may be accumulated by aquatic organisms or domestic animals. The bioaccumulative potential of this compound suggests that these may be important exposure pathways.

47.2.4 Other Sources of Human Exposure

Lindane is registered for commercial and home use as an insecticide. Its use in shampoo to combat lice results in direct exposure to consumers, while its commercial insecticidal uses may result in exposure through environmental media.

As reported above, lindane is found to some extent in drinking water, although generally at low levels. Air exposures are also possible, but again concentrations are low. Lindane was detected in 68% of ambient air samples taken from 16 U.S. cities in 1970-1972. The mean of the positive values was 0.9 ng/m^3 and the maximum was 11.7 ng/m^3 (992). In a 1980 survey of 10 U.S. cities, lindane was detected in 0.8% of the 123 samples, with a mean level of 0.1 ng/m^3 and a maximum value of 1.5 ng/m^3. Pankow et al. (1795) detected lindane in some samples of rain from a semi-rural and an urban site in Oregon. The mean dissolved rain concentrations were 0.45 ng/L and 11 ng/L, respectively. From these concentrations, the authors estimated equilibrium atmospheric gas phase concentrations of 6.3E-02 ng/m^3 and 1.5 ng/m^3. These data suggest that inhalation of lindane may occur in some locations at low levels.

Dietary intake, in general, also appears to be low. The average daily intake from market basket studies ranged from 0.002 to 0.004 mg/kg of body weight/day for adults over the years 1976-1979. The largest source in the diet was meat, fish and poultry (1245). The average daily intake for infants during this same time period was 0.001-0.006 mg/kg/day, and for toddlers it was 0.005-0.010 mg/kg/day for the same years (1244). Other specialized surveys have been conducted that show the presence of lindane at low levels in human milk (1249), and bovine and porcine fat samples (1248). It was not detected in a 1977 survey of bovine milk in Canada (1247). These data suggest that the diet represents a source of exposure to lindane, but exposures are generally low.

47.3 HUMAN HEALTH CONSIDERATIONS

47.3.1 Animal Studies

47.3.1.1 Carcinogenicity

Data on the carcinogenicity of lindane are inconclusive due to the varied response obtained from the numerous mouse strains and species of animals investigated.

Thorpe and Walker (1083) fed CF_1 mice 400 ppm lindane daily for 2 years. Liver enlargement was present by week 50 in both male and female mice. Examination of the liver at this stage revealed an irregular nodular surface with many lesions. The first liver tumor appeared in a treated female after 12 months, while the first tumor in a female control animal did not occur until 23 months. By the 110th week, 96% of the male mice fed 400 ppm lindane (compared with 24% in controls) and 95% of the female mice fed 400 ppm lindane (compared with 23% in controls) exhibited liver tumors. Hyperplastic nodules of the liver occurred in 38% of the treated males and 20% of the control males while hepatic neoplasms occurred in 55% of the treated males and only 4% in the control males. Hyperplastic nodules of the liver occurred in 34% of the treated females and 23% of the control females, while hepatic neoplasms occurred in 34% of the treated females and none of the control females. Thorpe and Walker concluded that prolonged ingestion of 400 ppm lindane induced a statistically significant increase in the incidences of hyperplastic foci and parenchymal cell tumors in the liver of CF_1 mice.

Weisse and Herbst (1082) studied the effect of lindane in the diet of Chbi:NMRI(SPF) mice in order to determine if the carcinogenic effect demonstrated in CF_1 mice was representative of the effects for all strains of mice. Male and female mice were given 0, 12.5, 25, or 50 ppm lindane in the diet for 80 weeks. There was no increased incidence of tumors in any of the treatment groups tested. A 19% incidence of tumor development did occur, however the frequency of occurrence was the same in all treatment groups. Weisse and Herbst concluded that lindane in doses of up to 50 ppm per day for 80 weeks in Chbi:NMRI(SPF) mice was not carcinogenic and produced no observable adverse effects.

Morrissey and Wolff (1117) investigated the effect of lindane on female (YS x VY)F hybrid mice grouped by color pattern into obese 1 yellow, lean pseudoagouti and lean black groups. Half of each group was fed 160 ppm lindane for 24 months. Lindane treatment resulted in 68.4%, 74.5% and 82.2% incidence of alveolar bronchiolization in yellow, pseudoagouti and black mice, respectively, in comparison to 14.7%, 10.5% and 10.4% in the color-matched controls. The incidence of alveolar cell tumors was statistically significant in lindane-treated, vy/a genetically identical (A) yellow (18.9%) and pseudogouti (13.8%) mice in comparison with 4.2% and 6.3% in the color-matched controls.

The NCI (1100) studied the effects of lindane on Osborne-Mendel rats and $B6C3F_1$ mice. Male rats were fed 236 or 472 ppm lindane while female rats were fed 135 or 270 ppm lindane. Rats were treated for 80 weeks and observed for 29-30 weeks. Male and female mice were fed 80 or 160 ppm lindane for 80 weeks and observed for 10-11 weeks. Body weight was not affected by lindane in any of the treated animals. Clinical signs of toxicity increased as the study progressed and by the last 6 weeks of the experiment, rats had rough and discolored hair coats, pale mucous membranes, dermatitis and vaginal bleeding. There was no significant increase in the incidence of tumors in the rats treated with lindane in comparison to the control animals. It was concluded that lindane was not carcinogenic in Osborne-Mendel rats at the levels administered in this study. Signs of toxicity in mice

included increased excitability, rough hair coats and abdominal distension. Hepatocellular carcinoma and neoplastic nodules of the liver were statistically significant in the low-dose male mice (39%) vs. the matched-control group (20%) or the pooled control group (10%). Due to a lack of dose-related response, NCI concluded that there was insufficient evidence of carcinogenicity in B6C3F$_1$ mice induced by lindane in this study.

IARC (25) evaluated all available literature on lindane carcinogenicity and concluded that there is sufficient evidence that lindane is carcinogenic in CF$_1$ mice. The carcinogenic nature of lindane in other strains and species is still in question. The low-dose treatment in the Weisse and Herbst (1082) and the NCI (1100) studies have led IARC to question the lack of response. IARC also noted the low number of control animals in the experimental groups in the NCI B6C3F$_1$ mice study.

47.3.1.2 Genotoxicity

Lindane has been shown to be non-genotoxic in all bacterial strains tested with or without activation (1101, 3027, 3276, 3649, 3575). Tsushimito et al (3730) observed that lindane did not induce mutations at the HPRT locus nor did it induce diphtheria toxin resistance mutants in Chinese hamster V79 cells treated in culture, but it did inhibit cell-to-cell communication or metabolic cooperation among these cells.

A 0.001% lindane solution produced no sex-linked recessive mutations when injected into Drosophila melanogaster (1102).

No unscheduled DNA synthesis occurred in SV40-transformed human fibroblasts (VA-1) (1105) or in Fischer 344 rat hepatocytes treated both with and without metabolic activation (3575). Rocchi et al. (1081) investigated the effect of lindane on scheduled and unscheduled DNA synthesis in the human lymphocyte. Lindane was shown to inhibit 72% of scheduled DNA synthesis and 55% of unscheduled DNA synthesis. Iverson et al. (3332) observed that lindane does not bind to DNA of mouse liver cells.

Lindane did cause a slight increase in the frequency of chromatid gaps and breaks in Chinese hamster fibroblasts in vitro (1103) and did inhibit cell division and produce chromatid breaks in human peripheral blood lymphocytes in vitro (1104).

Kiraly et al. (3357) did not observe an increase in chromosomal aberrations in lymphocytes of workers occupied in the production of lindane even though employees involved in the production of other pesticides did show increases.

47.3.1.3 Teratogenicity, Embryotoxicity and Reproductive Effects

Mametkuliev (1139) investigated the effect of lindane on pregnancy and teratogenicity. Rats were fed 0, 12 or 25 mg/kg lindane daily on days 1-20 of gestation. Other groups of rats were fed 25 mg/kg lindane daily on days 1-7 of

gestation or on days 7-15 of gestation. Examination of fetuses on day 20 revealed no teratogenic effect. However, animals fed 25 mg/kg lindane throughout pregnancy did show an increase in postimplantation death of embryos.

Palmer et al. (1079) studied the effect of lindane on fetal development in rabbits and rats. Lindane was intragastrically administered to pregnant New Zealand white rabbits and CFY rats at dosages of 5, 10, or 20 mg/kg body weight daily on gestational days 6-18 for the rabbit and 6-15 for the rat. All dams were slightly lethargic during the dosing period, but no other changes were observed. Examination of the rabbit offspring revealed a spontaneous malformation in only one fetus in the 10 mg/kg treatment group. There was a dose-related increase in the incidence of extra 14th ribs in the rat; however, it was not statistically significant. Palmer et al. concluded that lindane was not teratogenic or even embryotoxic in CFY rats or New Zealand white rabbits.

Recent studies (3119, 3252) agree that no effect on postnatal growth, viability, or postnatal maze activity testing on day 22 was observed in mice exposed by gavage to 25 mg/kg of lindane on days 8-12 of gestation.

In a 3-generation reproductive study, no malformations or compound related effects were reported in CD rats fed 25, 50, or 100 ppm lindane (1787). The significance of increased liver weight and enlarged hepatocytes in F_1 progeny was considered questionable.

47.3.1.4 Other Toxicologic Effects

47.3.1.4.1 Short-term Toxicity

Small amounts of lindane may cause dizziness, nausea, muscle weakness and tremors while a massive dose results in vomiting and diarrhea progressing to convulsions. Circulatory and respiratory failure may also appear (15). In the rat, the oral LD is listed as 76 mg/kg while the dermal LD_{50} is 500 mg/kg (51).

Frank and Braun (1085) reported 2 cases of accidental lindane ingestion in cattle. The first calf went into convulsions immediately after ingestion. It collapsed and died within one hour. The second calf developed convulsions 10 hours after ingestion. The convulsions persisted and increased in severity until the calf died 40 hours later. The esophagus was congested and the left lung was partially collapsed. It was later discovered that the calves had been given 3.6 g lindane. By examination of stomach content and tissue, it was determined that the first calf had consumed 2302 mg lindane while the second calf had consumed approximately 1100-1300 mg of lindane.

Cattabeni et al. (1087) examined the effect of lindane on the GABA (gamma-aminobutyric acid) system in rats. An alteration or decrease of GABA activity is correlated with convulsions and hyperexcitability. Male Sprague-Dawley rats were intraperitoneally injected with 100 mg/kg lindane and killed 10, 30 or 60 minutes later by microwave irradiation. Brains were examined and found to produce a statistically

significant time-dependent increase in GABA in the cerebellum (a 76% increase in 60 minutes). Cattabeni concluded that the convulsions triggered by lindane were not due to an interference with GABA metabolism. The mechanism of the convulsive seizures associated with lindane is still unknown; however, once the seizures have begun, the GABAergic system is activated, most likely as a form of protection.

Acetylcholinesterase (AChE) activity in plasma and synaptosomal fractions from the cervical cord, pons-medulla, cerebellum, midbrain, diencephalon and telencephalon were used as biochemical indices of toxicity for lindane-treated rats (3140). Male Wistar rats were administered (ip) 225 mg/kg lindane in corn oil. Controls received corn oil only. An additional group received lindane at 225 mg/kg but was also given an ip injection of succinylcholine (1 mg/kg) at the first signs of lindane intoxication. Lindane treatment resulted in hyperexcitability and tonic-clonic convulsions with death occurring at 38 minutes. Lindane treatment resulted in significant ($p < 0.001$) increases in AChE activity in plasma and all synaptosomal fractions. Succinylcholine reduced the lindane-induced hyperactivity and convulsions, and AChE activity in the midbrain and diencephalon. Succinylcholine increased AChE activity in the cervical cord, pons-medulla, cerebellum, and plasma. The authors concluded that AChE activity in the plasma may be used to differentiate between acute organophosphate and acute lindane intoxication.

Fishman and Gianutsos (3215) examined the role of cerebellar cyclic GMP in response to different isomers of hexachlorocyclohexane (HCH) including lindane (gamma-HCH). Cerebellar cyclic GMP levels were increased in mice one hour after administration of gamma-HCH (a seizure-producing isomer) at 80 or 120 mg/kg but not after 40 mg/kg. Alpha- and delta-HCH (non seizure-producing isomers) not only decreased cerebellar cyclic GMP accumulation but also prevented the gamma-HCH mediated increase in cyclic GMP. All HCH isomers inhibited the binding of 3H-TBOB (a ligand for the GABA-A-receptor linked chloride channel), indicating that the HCH effects on cerebellar GMP may be mediated through the GABA-A receptor linked chloride channel.

The effects of lindane on GABA were also studied by Tilson et al. (3718). It was reported that lindane (15 or 30 mg/kg, po) administered to male Fisher-344 rats produced significant decreases in the number of correct avoidance responses by these animals. Pretreatment with anticonvulsants such as phenobarbital and chlordiazepoxide which enhance GABA-mediated responses, blocked the disruptive effects of lindane on avoidance responses and also the seizures induced by higher (60 mg/kg) doses of lindane.

Male Wistar rats were treated with 800 ppm lindane for two weeks and then examined. Glucosuria accompanied by normal blood glucose was present in nearly all rats. The presence of glucose in the urine when levels of glucose in blood are normal, indicate a tubular defect in re-absorption. Urea is normally only partially re-absorbed through the tubules; however, in lindane-treated animals, there was an increase in the urinary urea and normal blood urea indicating a synthesis of urea in the renal tubules due to tissue destruction. Histopathological lesions were also

observed in the kidney as shown by hypertrophy and degradation of renal epithelium (1084).

Cats given lindane (1 or 2 mg/kg, iv) exhibited a dose-dependent hypoglycemic effect from 30 minutes to eight hours after administration. A sharp decrease in blood glucose at 30 minutes after dosing was attributed to the high energy demand during the lindane-induced convulsions. Hepatic glutathione (GSH) levels were lowered from four hours through eight hours after administration of the 2 mg/kg dose which corresponded to an increase in lindane content in the liver. The blood GSH level was significantly decreased from one to two hours after the 2 mg/kg lindane treatment, a time corresponding to the highest blood lindane levels. With respect to accidental human exposure to lindane, the authors noted the importance of the reduced blood glucose levels at times up to eight hours (3010).

The hematological parameters of male Wistar rats were studied when fed 800 ppm lindane for 2 weeks. Blood clotting time was significantly increased (44.3 seconds vs. 27 seconds in control animals). Other parameters, such as red and white blood cell counts, packed cell volume, hemoglobin and serum calcium, were not significantly affected by lindane (1086).

Lindane tends to accumulate in fatty tissue during administration. However, once exposure has ceased, lindane is eliminated from the body relatively quickly. Rats administered lindane accumulated 102 ppm in the fatty tissue. This level dropped to zero one week after lindane treatment was suspended (1156). Evaluation of rats fed 100 mg/kg lindane daily for 10 days showed that the body accumulation had diminished to 0.1 ppm only 3 days after treatment had ceased (1157).

The relationship between brain and blood lindane levels, and convulsant effects were reported by Tusell et al. (3733). An oral ED_{50} (84 mg/kg) and an ip ED_{50} (131 mg/kg) for lindane-induced tonic convulsions was determined following administration of 60 - 150 mg/kg to male Wistar rats. Characteristic neurotoxic effects were produced by all doses of lindane, and the incidence of the response was directly proportional to the log of the brain and blood lindane concentration. The oral and ip EC_{50} were 5.3 μl and 1.5 μl, respectively, and the threshold concentration for lindane-induced tonic seizures was estimated to be approximately 5 μg in the brain and approximately 1.5 μl in the blood. Kinetic analysis revealed that brain and blood lindane concentrations were highly correlated.

Reproductive toxicity of lindane was demonstrated for male rats receiving lindane at 4 or 8 mg/kg, ip over a period of 10 days (3123). The higher lindane dose resulted in a significant decrease in body weight and testicular weight relative to the control group. Additionally, the seminiferous lumens of the rats in the 8 mg/kg group were completely degenerated, and morphologically altered spermatocytes and spermatids were observed.

A dose-dependent decrease in sexual receptivity of female Fisher CDF-344 rats resulted from lindane administration (ip) at doses of 25, 33, 50, or 75 mg/kg on the

morning of proestrus. Most of the lindane-treated rats also failed to exhibit perceptive behavior (3756).

47.3.1.4.2 Chronic Toxicity

Heyroth (1155) reported results of long-term inhalation studies. Inhalation of lindane at 0.78 mg/m^3 by rats for 7 hours/day, 5 days/week for 180 days resulted in no adverse clinical signs. Necropsy revealed slight liver enlargement. Two of 20 rats exposed to 3% lindane dust for 7 hours/day, 5 days/week for 218 days developed some doubtful liver and kidney alterations (1155).

Male and female beagle dogs were fed 0, 25, 50, or 100 ppm lindane daily for 104 weeks. Ophthalmoscopic examination as well as hematological analyses were performed on weeks 4, 13, 26, 52, and 102. Urinalyses were conducted on a monthly basis. No clinical lindane-related effects were observed in any of the treated animals. Electroencephalogram (EEG), ophthalmological, hematological examinations and urinalyses were all normal. The only abnormal finding was that the dogs in the 100 ppm treatment group had unusually dark livers, but histological examination revealed no abnormalities. Animals were then dosed with 200 ppm lindane for 32 weeks in order to determine adverse effects at a higher level. Two animals developed convulsions by day 54 and 92. These convulsions were considered to be due to hereditary canine epilepsy rather than lindane toxicity. EEG's from this group revealed high voltage slow wave activity which was most likely indicative of non-specific neuronal irritation. It was concluded that no toxic effects could be contributed to chronic feeding of 50 ppm of lindane to beagle dogs (1088).

Due to the variable carcinogenic nature of lindane in rodents, Oesch et al. (1097) studied the effects of lindane on enzyme induction as a possible role of liver tumor promotion. CF_1 mice, $B6C3F_1$ mice and Osborne-Mendel rats were fed a diet containing approximately 0, 50, 120, and 270 ppm lindane for 3 days or 3 months. Enzyme activity and induction were not significantly different between the two mice strains, however, the $B6C3F_1$ mice did not survive the 3-month treatment with the highest dose of lindane. The CF_1 mice did differ enzymatically from Osborne-Mendel rats. At the 300 ppm treatment level, male and female CF_1 mice showed a very high monooxygenase activity compared to rats of both sexes. After treatment with the highest dose of lindane, CF_1 mice exhibited a lower epoxide hydrolase activity than the Osborne-Mendel rats, while a 5-6 fold increase in glutathione-S-transferase was seen. These variations in enzymes led Oesch et al. to speculate that the alterations of the enzymes involved in the metabolism of lindane in the liver may somehow relate to its carcinogenic nature in CF_1 mice (1097).

A study was conducted to ascertain the effects of long-term dietary exposure to lindane on its own biotransformation in various strains of mice, and whether or not any observed alterations in this metabolism could account for the varied susceptibility of rodents to lindane-induced hepatomas (3109). Obese yellow Avy/a, lean pseudo-agouti Avy/a, and lean black a/a phenotypes of (YS X VY) F_1 hybrid female mice were given dietary lindane (160 ppm) for 17, 30, 56, or 86 weeks. At the end of the

exposure period the mice were dosed po with 18 mg of lindane containing 55 μCi ^{14}U-lindane and a radiolabel inventory assessed for urine, feces, expired air, liver, kidney, fat, and blood samples. The 160 ppm lindane dietary exposure appeared to saturate the elimination pathways and increased the body burden of the pesticide and its metabolites. The study provided data indicating variability between rats and mice in the metabolism of lindane, and that the differences in lindane metabolism and disposition observed for the various mouse genotypes were associated with the chronic lindane treatment, aging, and obesity and not with the genotype.

47.3.2 Human and Epidemiologic Studies

47.3.2.1 Short-term Toxicologic Effects

Lindane poisoning in humans generally results from misuse or abuse of the 1% lindane preparation used to treat scabies and lice. Symptoms usually include vertigo, ataxia, agitation, tremors, headache, nausea, vomiting, respiratory failure and slower or unreactive pupils to light. Convulsions and coma are present in severely affected people (1098). The severity of the symptoms is usually determined by the serum concentration of lindane. Symptoms generally appear when blood levels reach 20 ng/ml while convulsions occur at a serum value of 290 ng/ml (1095).

Over a one month period, 79 people were affected by a 40% lindane mixture applied to bed covers, clothing, floors as well as the subjects' body surfaces. Initial symptoms included lassitude, headache, vertigo and muscle pain followed by intestinal colic, diarrhea, and stomatitis. Next, CNS symptoms appeared and were characterized by mental confusion, dysarthria (imperfect articulation of speech due to poor muscle control resulting from nervous system damage), and convulsions. Blindness from optic atrophy was observed in one individual and complaints of diminished vision were reported in two other cases. One death following degeneration of the liver and kidneys was also reported (1566).

Severe poisoning was reported in a sixteen-year-old boy following ingestion of 392 g of 1% lindane shampoo. He was found unconscious and taken to the hospital where gastric lavage was performed. A deep coma and convulsions ensued. Breathing was erratic and the pupils were only sightly reactive to light. Phenobarbital was given to control the seizures. He slowly recovered and was released from the hospital on the 12th day. Examination one month later was normal and seizures were reported to have disappeared completely by the fifth month (1089).

A poisoning by cutaneous exposure was reported by Davies et al. (1089). A two-month-old infant was treated for scabies with spot applications of lindane to the abdomen and legs for two days. The infant was then treated with a whole-body application of 1% lindane lotion after a hot bath. The lotion was left on the infant's skin for 18 hours and then washed off. The infant was found dead in his crib 24 hours later. Autopsy revealed 110 ppb lindane in the brain tissue, 33 ppb in the blood and 2.5 ppb in the urine. This is the first reported case of the brain level of lindane being 3 times greater than the blood level.

Another case of acute toxicity involved a 23-year-old man diagnosed with scabies. He completely covered his trunk and limbs with 1% lindane. Within 12 hours, symptoms included fatigue, dizziness, nausea and vomiting, difficulty with balance, slurred speech and general weakness. These symptoms cleared-up within 12 hours. The individual repeated the treatment one week later. After the second application, he lost consciousness three times but recovered after 24 hours (1090).

Pancytopenia, aplastic anemia, transient partial blindness in the left eye, dysarthria, and syncope were noted for a 14-year-old boy following topical application of 1% lindane lotion to skin with open lesions. Blood lindane concentration was reported as 9 μg/L two days after the incident and was <0.1 μg/L 16 days later. The authors indicated that the observed pancytopenia and aplastic anemia had not been previously reported for lindane intoxication (3062).

A 3-year 9-month-old boy with congenital ichthyosiform erythroderma was treated for scabies by topical application of a 1% lindane cream (3230). The boy was bathed 30 min prior to application of the lindane cream. Fifteen minutes after application, the patient developed nausea and vomiting lasting for one hour followed by twitching of the eyelids and fluttering of the eyes. Tonoclonic activity and unconsciousness followed about two hours later. The boy appeared normal the following morning, but 24 hours after the lindane application he developed unilateral twitching of facial muscles and rigidity of the legs for a period of approximately 30 minutes. Blood lindane level was 54 ng/mL at 72 hours after the lindane exposure. Blood chemistry values, EEG, and urinalysis were normal. No seizures or neurological disorders were noted one month after the lindane treatment. The author indicated that the blood lindane level was higher than normally reported (10 ng/mL) at 72 hours after exposure to 1% lindane, and that compromised epidermal barrier function (due to the warm bath or the erythroderma condition) may have accounted for increased lindane absorption and subsequent toxic reactions.

An interesting case of muscle degeneration involved a man who accidently ingested food seasoned with 15-30 mL lindane mistaken for monosodium glutamate. Thirty minutes later, he experienced grand mal seizures, nausea, vomiting and abdominal pain. Once in the hospital, he continued to have generalized tonic-clonic seizures for 2 hours. Blood analysis revealed severe metabolic acidosis and a lindane concentration of 600 ng/mL. Albuminuria and intense myoglobinuria were also present. An electroencephalogram (EEG) revealed diffuse intermittent disturbances of cerebral activity. By day 4, the patient was drowsy, had photophobia and complained of headaches and vertigo. The serum concentration of lindane had decreased to 5 ng/mL at this time. Muscles in the arms and legs were tender and serum urea nitrogen, creatinine, LDH and SGOT concentrations were substantially elevated. These results are indicative of muscle necrosis. The muscle damage was thought to occur due to the direct action of lindane on the muscle tissue. Renal failure associated with mild hyperkalemia and hyperuricemia also developed at this time. By day 15 of hospitalization, the patient's condition was greatly improved, however, the limb muscles were still weak and atrophic. A biopsy of the left deltoid muscle

revealed widespread areas of severe necrosis. Regeneration of muscle fibers was also present. The patient was released on the 24th day. Renal function, EEG and blood tests were all normal and muscular strength was improved. During the following year, the patient complained of difficulty with short-term memory, poor attention span, loss of libido and general weakness (1095).

47.3.2.2 Chronic Toxicologic Effects

Symptoms generally associated with prolonged use of a 1% lindane ointment include nausea, spasms, ataxia, and blood dyscrasia (1568). Occasional cases of aplastic anemia have also been reported following chronic lindane exposure (17).

Liver damage has been reported following long-term occupational exposure to lindane (1569). Eight workers heavily exposed to lindane, DDT or both for 5-13 years developed cirrhosis and chronic hepatitis.

Biochemical manifestations of toxic hepatitis were reported in 59 females and 29 males occupationally exposed to hexachlorocyclohexane (isomers not specified) over an 11-23 year period. The hepatobiliary system was effected in 55% of the workers while 33% developed chronic hepatitis. Chronic pancreatitis occurred in 5%. It was concluded that some form of biochemical abnormality occurred in at least 60% of those exposed (1398).

Tomczak et al. (1092) studied 54 male factory workers exposed for an average duration of 8 years to lindane during its production. Evaluation of sex hormones revealed a significant increase in serum luteinizing hormone (8.8 mIU/ml vs. 5.7 mIU/ml in the controls) while testosterone and follicle stimulating hormone levels remained normal. These results indicate an interference in sex hormone regulation. Further investigation is needed to establish if these alterations are of pathological significance.

Nervous system function was studied in this same group of factory workers by Baumann et al. (1093). Reflexes, forefinger tremor, electromyography and a manual skill tracking test were similar in the test and control groups. Despite years of exposure to lindane, no signs of neurological impairment or peripheral motor nerve damage were found.

Hematological effects resulting from chronic lindane exposure was reported by West (1106). A young girl was diagnosed with an atypical blood count and anemia. Examination of her family revealed four other members suffering from mild anemia. All recovered once a lindane vaporizer, which had been operating for 1.5 years, was removed from the home.

An increased incidence of lung cancer was reported between 1970 and 1975 in 285 agricultural workers spraying various pesticides including hexachlorocyclohexane (isomer not specified). Based on the potential for exposure to pesticides in addition to hexachlorocyclohexane, no evaluation on carcinogenicity was made. However, it

was concluded that the cancer incidence was too high to be attributed solely to smoking and further investigation was recommended (1432).

An unusual case of acute myeloblastic leukemia, secondary to aplastic anemia was associated with dermal exposure to a lindane pesticide mixture. A male patient was hospitalized due to left lobar pneumonia. Bone marrow aspiration and bone biopsy revealed marked hypoplastic anemia. It was discovered at this time that the patient worked in a small unventilated bookstore for the past 15 years where he frequently used large amounts of insecticide. The insecticide mixture contained lindane, piperonyl butoxide and pyrethrum in kerosene, xylene and toluene. The man was treated with antibiotics and leukocyte transfusions. His condition gradually improved. Three months later, his hemoglobin level dropped to 7.5 g/100 mL (13-18 g/100 mL is the normal range) and he was given blood transfusions. Bone marrow aspiration revealed aplastic anemia. The patient refused to follow warnings to discontinue use of the insecticide and within one month acute myeloblastic leukemia was diagnosed. The patient died soon after from septicemia. Even though the pesticide contained a variety of compounds, lindane was thought to be the main reason for the anemia and leukemia (1099).

47.3.3 Levels of Concern

Based on the induction of liver tumors in male CF_1 mice fed 400 ppm lindane for 110 weeks, the USEPA has specified an ambient water quality criterion for this compound of zero. In that attaining a zero concentration level may be infeasible in some cases, the concentrations of lindane in water calculated to result in incremental lifetime cancer risks of 1E-05, 1E-06, and 1E-07 from ingestion of both water and contaminated aquatic organisms were estimated to be 186, 18.6 and 1.86 ng/L, respectively (355). Risk estimates are expressed as a probability of cancer after a lifetime consumption of two liters of water per day and consumption of 6.5 g of fish per day containing a specified concentration of the contaminant. Thus, a risk of 1E-05 implies that a lifetime daily consumption of two liters of drinking water and 6.5 g of contaminated fish at the criterion level of 186 nanograms lindane per liter would be expected to produce one excess case of cancer above the normal background incidence for every 100,000 people exposed. It should be emphasized that these extrapolations are based on a number of assumptions and should be taken as crude estimates of human risk at best.

Under the National Primary Drinking Water Regulations (296), the maximum contaminant level for lindane in drinking water is 4 μg/L. The USEPA has proposed a reduction in this value to 0.2 μg/L (3883).

The WHO (666) recommends a health based guideline of 3 μL for lindane in drinking water.

OSHA (3539) currently permits and the ACGIH (3005) recommends exposure be limited to 0.5 mg/m^3 lindane averaged over an 8-hour work-shift.

IARC (803) lists lindane in category 2B (sufficient evidence in animals) in its weight-of-evidence ranking of potential carcinogens.

47.3.4 Hazard Assessment

Dietary administration of lindane induced liver tumors in male CF_1 mice (1083); tests conducted with other mouse strains and rats were negative (1082, 1100). Based on the findings in CF_1 mice, the USEPA (667) calculated an upper-limit incremental unit cancer risk of 1.33E-01 (mg/kg/day) for lindane.

Limited evidence exists to indicate potential mutagenic capability for lindane. Lindane did induce chromatid breaks in human lymphocytes and Chinese hamster fibroblasts in culture (1104, 1103) but produced no sex-linked recessive lethal mutations in Drosophila (1102) or mutations in bacterial assays (1101).

No adverse effects were noted in a 3-generation study with rats fed lindane at a concentration of 100 ppm (1787). Other studies indicate no embryotoxic or teratogenic effects in either rats or rabbits administered 20 mg/kg by gavage during gestation (1079). Another study indicated possible embryotoxic effects in rats exposed to 25 mg/kg daily throughout gestation (1139).

The primary response to lindane is stimulation of the CNS, resulting in hyperexcitability and convulsions. Lindane is the most acutely toxic of the hexachlorocyclohexane isomers (12). The oral and dermal LD_{50} values for the rat are 76 mg/kg and 500 mg/kg, respectively (51). Long-term exposures result in pathological changes in liver and kidney; rats fed 800 ppm lindane in the diet for two weeks exhibited kidney damage (1084). The no-adverse-effect levels for both the rat (1082) and dog (1088) in 2 year dietary exposure studies were 50 ppm.

Effects of lindane intoxication in humans include repeated, clonic convulsions, respiratory difficulty and cyanosis. Fatalities have been documented (1566, 1089, 1099). Ingestion of large doses have led to muscle and kidney necrosis (1095). Chronic exposure to lindane has been linked to anecdotal reports of aplastic anemia (17) and possible pancreatitis in workers exposed to an unspecified isomer of hexachloro- cyclohexane (1398).

47.4 SAMPLING AND ANALYSIS CONSIDERATIONS

Determination of lindane (gamma BHC) concentrations in soil and water requires collection of a representative field sample and laboratory analysis. Care is required to prevent losses during sample collection and storage. Soil and water samples should be collected in glass containers; extraction of samples should be completed within 7 days of sampling and analysis completed within 40 days. In addition to the targeted samples, quality control samples such as field blanks, duplicates, and spiked matrices may be specified in the recommended methods.

EPA-approved procedures for the analysis of lindane, one of the EPA priority pollutants, in aqueous samples include EPA Methods 608, 625 (65), 8080, and 8250 (63). Prior to analysis, samples are extracted with methylene chloride as a solvent using a separatory funnel or a continuous liquid-liquid extractor. The concentrated sample extract is solvent exchanged into hexane and an aliquot of the hexane extract injected onto a gas chromatographic (GC) column using a solvent flush technique. The GC column is programmed to separate the semi-volatile organics; lindane is then detected with an electron capture detector or halogen specific detector, (Methods 608 and 8080) or a mass spectrometer (Methods 625 and 8250). Automated interpretation of mass spectra has been evaluated for this compound and other pesticides (3017). Capillary columns have also been used for GC separations (3356, 3404) in addition to packed columns.

The EPA procedures recommended for lindane analysis in soil and waste samples, Methods 8080 and 8250 (63), differ from the aqueous procedures primarily in the preparation of the sample extract. Solid samples are extracted using soxhlet extraction or sonication methods. Neat and diluted organic liquids may then be analyzed by direct injection.

It may be necessary to cleanup the sample extracts to remove impurities that interfere with the final analysis. Gel permeation chromatography (GPC) (Method 3640), column adsorption chromatography (Method 3620), or various techniques for removing sulfur (Method 3660) may be used in this case prior to GC/electron capture or GC/mass spectrometric analysis. Interferences from phthalates may be minimized by avoiding sample contact with all plastic materials. The microcoulometric and electrolytic conductivity detectors are more selective and will eliminate interferences from phthalate esters. It was also noted in Method 8250 that alkaline extraction conditions may result in decomposition of lindane. For the determination of this compound neutral extraction should be used.

Typical lindane detection limits that can be obtained in waste-waters and nonaqueous samples (wastes, soils, etc.) are shown below. The actual detection limit achieved in a given analysis will vary with instrument sensitivity and matrix effects. Detection limits using Methods 625 and 8250 were not indicated.

Aqueous Detection Limit	Nonaqueous Detection Limit
0.04 µg/L (Method 8080) 0.004 µg/L (Method 608)	2.7 µg/kg (Method 8080 with GPC cleanup)

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Note: The nonsequential numbers of the references reflect the order of references as they appear in the master bibliography.

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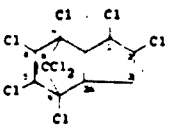
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COMMON SYNONYMS:	CAS REG.NO.:FORMULA:	AIR W/V CONVERSION FACTOR at 25°C (12)
1,2,4,5,6,7,8,8-Octachloro-2,3,3a,4,7,7a-hexahydro-4,7-methano-1h-indene Chlordane Dichlorochlordene	57-74-9 $C_{10}H_6Cl_8$ NIOSH NO: PB9800000 STRUCTURE: 	16.75 mg/m³ ≈ 1 ppm; 0.0596 ppm ≈ 1 mg/m³ MOLECULAR WEIGHT: 409.8

REACTIVITY	Chlordane is considered to be a halogenated organic compound for compatibility classification purposes. Halogenated organic compounds typically generate heat in reactions with cyanides, mercaptans, and other organic sulfides. Those with non-oxidizing mineral acids, amines, and strong oxidizing agents typically evolve heat and toxic gases, while those with caustics or nitrides evolve heat and flammable gases. Reactions with oxidizing mineral acids may generate heat, toxic gases, and fire, while those with azo or diazo compounds or hydrazines may evolve heat and usually innocuous gases. Certain elemental metals and alloys such as sheets, rods, drops, etc., may evolve heat and fire in reactions with these compounds, while alkali and alkaline earth elemental metals and metals as powders, vapors, or sponges may evolve heat and initiate an explosion. Heat and explosion are also possible results of reactions with organic peroxides, organic hydroperoxides, or strong reducing agents (511).

PHYSICO-CHEMICAL DATA (technical grade)	• Physical State: Liquid, viscous (at 20°C)	(23)
	• Color: Colorless to amber	(51)
	• Odor: Slightly pungent, like chlorine	(60)
	• Odor Threshold: No data	
	• Density: 1.6000 g/mL (at 25°C)	(60)
	• Freeze/Melt Point: 103.00 to 108.80°C	(10)

PHYSICO-CHEMICAL DATA (Cont.)	• Boiling Point: 175.00°C at 2 mm Hg	(38)
	• Flash Point: Not flammable	(38,60)
	• Flammable Limits: Not	(38,60)
	• Autoignition Temp.: Not flammable	(38,60)
	• Vapor Pressure: 1.00E-05 mm Hg (at 20°C)	(38)
	• Satd. Conc. in Air: 2.2000E-01 mg/m^3 (at 20°C)	(1219)
	• Solubility in Water: 5.60E-02 mg/L (at 25°C)	(33)
	• Viscosity: 58.000 cp (at 54°C)	(60)
	• Surface Tension: 2.5000E+01 dyne/cm (at 20°C)	(60)
	• Log (Octanol-Water Partition Coefl.): 5.48	(33)
	• Soil Adsorp. Coeff: 3.80E+04	(1210)
	• Henry's Law Const.: 2.20E-04 $atm \cdot m^3/mol$ (at 25°C)	(1531)
	• Bioconc. Factor: 1.41E+04	(993)

PERSISTENCE IN THE SOIL-WATER SYSTEM	Expected to be fairly immobile in the soil/ground-water system due to strong sorption and moderate volatilization. Data on degradation are limited, expected to be moderately persistent. Risk of groundwater contamination moderate; contamination of surface waters by surface runoff reported.

PATHWAYS OF EXPOSURE	Pathways of concern from the soil/ground-water system are migration to ground water drinking water supplies, uptake by crops from soil and bioaccumulation by aquatic organisms or domestic animals. Soil application of chlordane may also result in contamination of indoor air of slab- on-grade homes.

HEALTH HAZARD DATA	Signs and Symptoms of Short-term Human Exposure: (38) Exposure may cause shaking, blurred vision, irritability, confusion, delirium, staggering, convulsions and death. Ingestion may cause nausea, vomiting and diarrhea. Absorption through the skin is rapid and has resulted in death. Acute Toxicity Studies: (3504) INHALATION: LC_{xx} 100 mg/m³ · 4 hr — Cat ORAL: LD_{xx} 200 mg/kg — Rat LD_{Lo} 0.1 mg/kg — Woman TD_{Lo} 3.07 mg/kg — Man SKIN: LD_{xx} 780 mg/kg — Rabbit LD_{Lo} 428 mg/kg — Human Long-Term Effects: Kidney and liver damage Pregnancy/Neonate Data: Decreased fertility Genotoxicity Data: Conflicting data Carcinogenicity Classification: IARC - Group 3 (not classifiable as to its carcinogenicity to humans) NTP - Positive mice EPA - Group B2 (probable human carcinogen; sufficient evidence in animals and inadequate evidence in humans)

HANDLING PRECAUTIONS (38,54,60)	Handle chemical only with adequate ventilation • Vapor concentrations of 0.5 to 5 mg/m³ : any supplied air respirator, self-contained breathing apparatus or chemical cartridge respirator with an organic vapor cartridge • 5-25 mg/m³: any supplied air respirator or self-contained breathing apparatus with full facepiece; a chin-style or frontor backmounted pesticide protective mask; a chemical cartridge respirator with a full facepiece and organic vapor cartridge • Chemical goggles if there is probability of eye contact • Appropriate neoprene clothing to prevent repeated or prolonged skin contact.

ENVIRONMENTAL AND OCCUPATIONAL STANDARDS AND CRITERIA

AIR EXPOSURE LIMITS:

Standards
- OSHA TWA (8-hr): 0.5 mg/m³ (skin)
- AFOSH PEL (8-hr TWA): 0.5 mg/m³; STEL (15-min): 1.5 mg/m³ (skin)

Criteria
- NIOSH IDLH (30-min): 500 mg/m³
- ACGIH TLV® (8-hr TWA): 0.5 mg/m³ (skin)
- ACGIH STEL (15-min): Deleted

WATER EXPOSURE LIMITS:

Drinking Water Standards (3883)
MCLG: 0 µg/L (proposed)
MCL : 2 µg/L (proposed)

EPA Health Advisories and Cancer Risk Levels (992)
The EPA has developed the following Health Advisories which provide specific advice on the levels of contaminants in drinking water at which adverse health effects would not be anticipated.

- 1-day (child): 60 µg/L
- 10-day (child): 60 µg/L
- longer-term (child): 0.5 µg/L
- longer-term (adult): 0.5 µg/L
- 1E-04 cancer risk level: 3 µg/L

WHO Drinking Water Guideline (666)
A health-based guideline for drinking water of 0.3 µg/L is recommended for chlordane (total isomers). A daily per capita consumption of two liters of water was assumed.

EPA Ambient Water Quality Criteria
- Human Health (355)
  - Based on ingestion of contaminated water and aquatic organisms, (1E-05, 1E-06, 1E-07 cancer risk), 4.6 ng/L, 0.46 ng/L, 0.046 ng/L.
  - Based on ingestion of contaminated aquatic organisms only, (1E-05, 1E-06, 1E-07 cancer risk), 4.8 ng/L, 0.48 ng/L, 0.048 ng/L.
  - Based on ingestion of contaminated water only, (1E-05, 1E-06, 1E-07 cancer risk), 3.0 µg/L, 0.3 µg/L, 0.03 µg/L.

ENVIRONMENTAL AND OCCUATIONAL STANDARDS AND CRITERIA (Cont.)

- Aquatic Life (355)
  - Freshwater species
    The criterion to protect freshwater aquatic life as derived using the guidelines is 0.0043 µg/L as a 24-hour average and the concentration should not exceed 2.4 µg/L at any time.

  - Saltwater species
    The criterion to protect saltwater aquatic life as derived using the guidelines is 0.0040 µg/L as a 24-hour average and the concentration should not exceed 0.09 µg/L at any time.

REFERENCE DOSES:
ORAL: 4.500E-02 µg/kg/day (3744)

REGULATORY STATUS (as of 01-MAR-89)

Promulgated Regulations

- Federal Programs

Clean Water Act (CWA)
Chlordane is designated a hazardous substance. It has a reportable quantity (RQ) of 0.454 kg (347, 3764). It is also listed as a toxic pollutant, subject to general pretreatment regulations for new and existing sources, and effluent standards and guidelines (351, 3763). Effluent limitations specific to this chemical have been set in the following point source categories: electroplating (3767), pesticide chemicals (891), and steam electric power generating (3802). Effluent limitations in the pesticide chemicals manufacturing category are set at 0.010 kg/1000 kg of organic pesticide chemicals (including chlordane) maximum for any one day (891). Limitations in the other point source categories depend on the type of plant and industry.

Safe Drinking Water Act (SDWA)
Chlordane is on the list of 83 contaminants required to be regulated under the SDWA of 1974 as amended in 1986 (3781). In states with an approved Underground Injection Control program, a permit is required for the injection of chlordane (technical)- containing wastes designated as hazardous under RCRA (295).

Resource Conservation and Recovery Act (RCRA)
Chlordane (technical) is identified as a hazardous waste (U036) and listed as a hazardous waste constituent (3783, 3784). Waste streams from the following industry contain chlordane and are listed as specific sources of hazardous wastes: pesticides (chlordane production) (3774, 3765). Effective July 8, 1987, the land disposal of untreated hazardous wastes which contain halogenated organic compounds in total concentrations greater than or equal to 1000 mg/kg is prohibited. Effective August 8, 1988, the underground injection into deep wells of these wastes is prohibited, and EPA requires incineration of them in accordance with the requirements of 40CFR264.343 or 265.343. Certain variances exist until May, 1990 for some wastewaters and nonwastewaters for which Best Demonstrated Available Technology (BDAT) treatment standards have not been promulgated by EPA (3786, 3782). Chlordane is also included on EPA's ground-water monitoring list. EPA requires that all hazardous waste treatment, storage, and disposal facilities monitor their ground-water for chemicals on this list when suspected contamination is first detected and annually thereafter (3775).

Comprehensive Environmental Response Compensation and Liability Act (CERCLA)
Chlordane is designated a hazardous substance under CERCLA. It has a reportable quantity (RQ) limit of 0.454 kg. Reportable quantities have also been issued for RCRA hazardous waste streams containing chlordane but these depend upon the concentrations of the chemicals in the waste stream (3756). Chlordane is designated an extremely hazardous substance under SARA Title III Section 302. Any facility at which chlordane is present in excess of its threshold planning quantity of 1000 pounds must notify state and local emergency planning officials. If chlordane is released from the facility in excess of its reportable quantity (RQ), local emergency planning officials must be notified (3766). Under SARA Title III Section 313, manufacturers, processors, importers, and users of chlordane must report annually to EPA and state officials their releases of this chemical to the environment (3787).

Federal Insecticide, Fungicide and Rodenticide Act (FIFRA)
Action levels for chlordane and its degradation products in agricultural commodities range from 0.1 to 0.3 ppm (973). Pesticide registration standards for chlordane have been issued by EPA (3798).

Marine Protection Research and Sanctuaries Act (MPRSA)
Ocean dumping of organohalogen compounds as well as the dumping of known or suspected carcinogens, mutagens or teratogens is prohibited except when they are present as trace contaminants. Permit applicants are exempt from these regulations if they can demonstrate that such chemical constituents are non-toxic and non-bioaccumulative in the marine environment or are rapidly rendered harmless by physical, chemical or biological processes in the sea (309).

Occupational Safety and Health Act (OSHA)
Employee exposure to chlordane shall not exceed an 8-hour time-weighted average (TWA) of 0.5 mg/m³. Employee skin exposure to chlordane shall be prevented/reduced through the use of protective clothing and practices (3539).

Hazardous Materials Transportation Act (HMTA)
The Department of Transportation has designated chlordane(technical) as a hazardous material with a reportable quantity of 0.454 kg, subject to requirements for packaging, labeling and transportation (3180).

- State Water Programs

ALL STATES
All states have adopted EPA Ambient Water Quality Criteria and NPDWRs (see Water Exposure Limits section) as their promulgated state regulations, either by narrative reference or by relisting the specific numeric criteria. These states have promulgated additional or more stringent criteria:

ARKANSAS
Arkansas sets a chronic toxicity standard of 0.0043 µg/L (24-hr. average) for chlordane in surface waters, and an acute toxicity standard of 2.4 µg/L (never to exceed) for the protection of human, animal, plant and aquatic life (3587).

CALIFORNIA
California has an action level of 0.055 µg/L for chlordane in drinking water (3098). California also sets a drinking water standard of 3 µg/L for Municipal and Domestic Use Region 1 and 5 waters, and 4 µg/L for Ocean Plan waters (3097).

FLORIDA
Florida requires that the level of chlordane not exceed 0.01 µg/L for Class I and III fresh surface waters and 0.004 µg/L for Class II and III marine surface waters (3220).

ILLINOIS
Illinois has a criterion of 0.003 mg/L for chlordane in the public water supply (3322).

KANSAS
Kansas has an action level of 0.27 µg/L for ground-water (3213).

LOUISIANA
Louisiana has a water quality criterion of 2.4 µg/L for fresh surface water and 4.6 ng/L for public waters (3406).

NEW HAMPSHIRE
New Hampshire sets an enforceable Toxic Contaminant Level (TCL) for chlordane in drinking water of 63 μg/L for a one-day exposure (assumes a child weighing 10 kg who drinks one liter of water per day) (3710).

NEW JERSEY
New Jersey has set an MCL of 0.5 μg/L for chlordane in drinking water (3497).

NEW YORK
New York sets an MCL of 5 μg/L for drinking water, a water quality standard of 0.1 μg/L for ground-water classed for drinking water supply, and a nonenforceable water quality guideline of 0.02 μg/L for surface waters (3501).

OKLAHOMA
Oklahoma requires that the instream concentration of chlordane not exceed 0.02 μg/L in surface waters classed for fish and wildlife propagation (3534).

VERMONT
Vermont has a preventive action limit of 0.0027 μg/L and an enforcement standard of 0.027 μg/L for chlordane in ground-water (3682).

VIRGINIA
Virginia has set a water quality standard of 0.01 μg/L for ground-water (3135).

WEST VIRGINIA
West Virginia currently has a water quality criterion of 4.3 ng/L for public waters, but has proposed new criteria that are the same as federal criteria. These new criteria will be promulgated by late spring 1989 (3835).

Proposed Regulations

- Federal Programs

Safe Drinking Water Act (SDWA)
EPA will propose a maximum contaminant level goal (MCLG) of zero and a maximum contaminant level (MCL) of 0.002 mg/L for chlordane in May, 1989, with final action scheduled for May, 1990 (3759).

Resource Conservation and Recovery Act (RCRA)
EPA has proposed that solid wastes be listed as hazardous because they exhibit the characteristic defined as EP toxicity when the TCLP extract concentration is equal to or greater than 0.03 mg/L chlordane. Final promulgation of this Toxicity Characteristic Rule is expected in June, 1989 (1565).

- State Water Programs

MOST STATES

Most states are in the process of revising their water programs and proposing changes to their regulations which will follow EPA's changes when they become final. Contact with the state officer is advised. Changes are projected for 1989-90 (3683).

MINNESOTA

Minnesota has proposed a Recommended Allowable Limit (RAL) of 0.3 µg/L for chlordane in drinking water (3451). Minnesota has also proposed Sensitive Acute Limits (SAL) of 1.7 µg/L for cold surface waters and 1.2 µg/L for other designated surface waters, and chronic criteria of 0.001 µg/L for designated surface waters and 0.3 µg/L for designated ground-waters. These criteria are for the protection of human health (3452).

EEC Directives

Directive on Drinking Water (533)

The mandatory values for total pesticides in surface water treatment categories A1, A2 and A3 used or intended for abstraction of drinking water are 0.001, 0.0025 and 0.005 mg/L, respectively. There are no guideline values

Directive Relating to the Quality of Water for Human Consumption (540)

The maximum admissible concentration for chlordane is 0.1 µg/L. The total maximum allowable concentration for pesticides and related products is 0.5 µg/L.

Directive on Ground-Water (538)

Direct discharge into ground-water (i.e., without percolation through the ground or subsoil) of organophosphorous compounds, organohalogen compounds and substances which may form such compounds in the aquatic environment, substances which possess carcinogenic, mutagenic or teratogenic properties in or via the aquatic environment and mineral oils and hydrocarbons is prohibited. Appropriate measures deemed necessary to prevent indirect discharge into ground-water (i.e., via percolation through ground or subsoil) of these substances shall be taken by member countries.

Directive on Bathing Water Quality (534)

When inspection of a bathing area shows that heavy metals, pesticides or cyanides may be present, concentrations should be checked by competent authorities.

Directive on the Quality Required of Shellfish Waters (537)
The mandatory specifications for organohalogenated substances specify that the concentration of each substance in the shellfish water or in shellfish flesh must not reach or exceed a level which has harmful effects on the shellfish and larvae. The guideline specifications for organohalogenated substances state that the concentration of each substance in shellfish flesh must be so limited that it contributes to the high quality of shellfish product.

Directive on the Discharge of Dangerous Substances (535)
Organohalogens, organophosphates, petroleum hydrocarbons, carcinogens or substances which have a deleterious effect on the taste and/or odor of human food derived from aquatic environments cannot be discharged into inland surface waters, territorial waters or internal coastal waters without prior authorization from member countries which issue emission standards. A system of zero- emission applies to discharge of these substances into ground-water.

Directive on Marketing and Use of Dangerous Substances (541)
Chlordane may not be used in ornamental objects intended to produce light or color effects by means of different phases.

Directive on Classification, Packaging and Labeling of Pesticides (786)
Chlordane is listed as a Class II/b substance and is subject to packaging and labeling regulations.

Directive on the Classification, Packaging and Labeling of Dangerous Substances (787)
Chlordane is classified as a harmful substance and is subject to packaging and labeling regulations.

Directive on Plant Protection Products (1333)
Plant protection products containing chlordane may be neither placed on the market nor used. If it appears necessary, because of an unforeseeable danger threatening plant production which cannot be controlled by other means, such products may be permitted to be marketed and/or used for a maximum period of 120 days.

EEC Directives - Proposed Proposal for a Council Directive on the Dumping of Waste at Sea (1793)
EEC has proposed that the dumping of pesticides at sea be forbidden without prior issue of a special permit. The dumping areas shall be designated in the permits.

Resolution on a Revised List of Second-Category Pollutants (545)
Chlorodane is one of the second-category pollutants to be studied by the Commission in the programme of action of the European Communities on Environment in order to reduce pollution and nuisances in the air and water. Risk to human health and the environment, limits of pollutant levels in the environment, and determination of quality standards to be applied will be assessed.

EEC Directives - Regulation
Council Regulation Concerning Export and Import Into the Community of Certain Dangerous Chemicals (1795)
EEC requires that any third country export of chlordane on its own or in preparations must be reported by the exporter to a designated authority in the state of export and the state of import. The product must be packaged and labeled in accordance with the Directive on Classification, Packaging and Labeling of Dangerous Substances. The designated authority should forward to the Commission all notification and relevant information as indicated in Article 7 of this regulation.

48.1 MAJOR USES

Chlordane has been used extensively over the past 30 years for termite control, as an insecticide for homes and gardens and as a control for soil insects during crop production (54). Both the uses and production volume have decreased since the Environmental Protection Agency issued a registration suspension notice for all food crops and home and garden uses in 1978 (54). Its use is now restricted to subsurface ground insertion for termite control (994).

A general concern with the data available on chlordane is the purity of the material. Most often, technical-grade material has been used. Technical chlordane is composed of approximately 24% trans-chlordane, 19% cis-chlordane, 21.5% chlordane isomers, 10% heptachlor, 7% nonachlor, and 18.5% related chlorinated hydrocarbons (993). Improvements in manufacturing have resulted in products containing 75% trans- and 25% cis-chlordane and less than 1% heptachlor (59). Additionally, a certain degree of confusion exists due to the use of three different nomenclature systems: cis- and trans-chlordane are equivalent, respectively, to alpha- and gamma-chlordane as used by the manufacturer and beta and alpha chlordane as used by various investigators. The terms cis and trans have been used throughout this chapter whenever it was possible to identify the isomer in question.

48.2 ENVIRONMENTAL FATE AND EXPOSURE PATHWAYS

48.2.1 Transport in Soil/Ground-water Systems

48.2.1.1 Overview

Technical chlordane, commonly used as an insecticide, is a complex mixture of many chlorinated components, having different persistence patterns in the environment. The major components include cis-chlordane, trans-chlordane, heptachlor, and nonachlor. Most environmental studies have focused on the two major chlordane isomers and the persistence of technical chlordane is approximated by the behavior of these two components. After application of technical chlordane in soil, successive analyses for residues showed rapid disappearance of all minor components, leaving only cis-chlordane and trans-chlordane (1532). Other studies (1243, 1498) have shown significant soil residues as well as residual indoor air concentrations after application of technical chlordane. In this chapter, discussion will be limited to the environmental fate of the cis- and trans-chlordane isomers.

Chlordane is expected to be relatively immobile in the soil/ground-water system when present at low concentrations. Bulk quantities of the liquid chemical (e.g., from a spill, heavy spray application, or improper disposal of excess formulations) could be transported through the unsaturated zone. However, most studies have shown that

proper application of chlordane to soil surfaces does not result in rapid transport through the soil. Furthermore, as discussed later in this section, chlordane may be susceptible to degradation in the soil/ground-water system.

In general, transport pathways can be assessed by using an equilibrium partitioning model, as shown in Table 48-1. These calculations predict the partitioning of low soil concentrations of chlordane among soil particles, soil water and soil air. Portions of chlordane associated with the water and air phases of the soil have higher mobility than the adsorbed portion. Estimates for the unsaturated topsoil model indicate that almost all (99.9%) of the chlordane is expected to be associated with the stationary phase. Much less than 1% is expected to partition to the soil-water phase; therefore, only a small portion would be available to migrate by bulk transport (e.g., the downward movement of infiltrating water), dispersion and diffusion. An insignificant portion of the chlordane is expected in the gaseous phase of the soil; diffusion of vapors through the soil-air pores up to the ground surface is not expected to be important (other data shown below indicate that volatilization at the surface may be enhanced by soil moisture). In saturated, deep soils (containing no soil air and negligible soil organic carbon), the percentage of the chlordane predicted to be present in the soil-water phase (Table 48-1) and available for transport with flowing ground water is expected to be fairly small. Based on this model, ground water underlying chlordane-contaminated soils with low organic content is not expected to be vulnerable to contamination.

Due to chlordane's extensive use as an insecticide, several investigators have studied its persistence in soil (1210, 1531, 1532, 994, 1533). In general, these studies show that chlordane is quite persistent and transport with soil water (leaching) is low; volatilization - at least at the surface - may be important. The reported leaching index for chlordane suggests less than 10 cm movement through soil with rainfall of 150 cm per year (1539).

Half-lives of chlordane in soil have been reported to range from two years to eight years (1532, 1211, 1540, 1541). Persistence data reported by other investigators (1542-1544) suggest that the longer half-lives are more probable. The lowest persistence (9% after 16 years) was reported in a study using very heavy application rates (112 kg/ha and 224 kg/ha) on sandy loam soil.

Soil monitoring studies have measured chlordane residues (ppb to ppm levels) in significant percentages of sampled farm lands, urban areas and residential areas. Uptake of chlordane by plants is generally thought to be limited to absorption by plant roots (1537) and has been shown to be related to soil type (994). No chlordane residues were detected in seeds from any crop (1533); however, one study (1538) reported translocation of chlordane into alfalfa foliage. In most temperate climates, only the cis-and trans-chlordane isomers persist after application of technical chlordane; however, in colder climates, the residues more closely resemble the technical chlordane mixture (994).

TABLE 48-1
EQUILIBRIUM PARTITIONING CALCULATIONS FOR CHLORDANE IN MODEL ENVIRONMENTS [a]

Soil Environment	Estimated Percent of Total Mass of Chemical in Each Compartment		
	Soil	Soil-Water	Soil-Air
Unsaturated topsoil at 25°C[c]	99.9	0.01	1E-04
Saturated deep soil[d]	99.4	0.6	-

a) Calculations based on Mackay's equilibrium partitioning model (34, 35, 36); see Introduction in Volume 1 for description of model and environmental conditions chosen to represent an unsaturated topsoil and saturated deep soil. Calculated percentages should be considered as rough estimates and used only for general guidance.
b) Utilized estimated soil sorption coefficient (1210): K_{oc} = 38,000.
c) Henry's law constant taken as 2.2E-04 atm·m³/mol at 25°C (1531).
d) Used sorption coefficient $K_p = 0.001 \times K_{oc}$

48.2.1.2 Sorption on Soils

Values of the equilibrium soil sorption constant, K_{oc}, for chlordane have been reported as 21,300 (812), 38,000 (1210), and 140,000 (33). These values indicate that chlordane will be fairly strongly sorbed onto soils with organic content >0.1%. As with all neutral organic chemicals, the extent of sorption is proportional to the soil organic content. For low organic carbon soils (e.g., <0.1%), the extent of sorption may also depend on properties such as surface area, cation exchange capacity and degree of hydration.

Several investigators have examined the vertical and horizontal transport of chlordane applied to soil surfaces; most of the residue has been reported to be in the immediate vicinity of the treated area and migration below the surface was minimal. Examination of soil adjacent to the walls of a house treated with chlordane after construction (1543) indicated that 99% to 100% of the residue was in the top 10 inches. The horizontal distribution showed that 40%, 19%, 20%, 17%, and 3% of the residue was found 0.5, 1, 2, 4, and 10 feet from the building, respectively; essentially, no residue was detected below the surface. In soil transport experiments

using sand and loam soil columns to which 2.5 liters of water were added over 80 days, 99.5% to 100% of the applied chlordane was retained in the top 10 cm (1546). The same authors also examined soil core samples after chlordane application and found about 88% of the residue in the top 7.5 cm and another 10% of the residue 7.5-15 cm below the surface. Some leaching of chlordane from three treated surface soils to untreated sandy subsurface soil under field conditions has been reported (1547). Approximately 50% of the applied material in sand and loam leached into subsurface soil after 6-12 months, while 33% of the material in clay soils leached into subsurface soils during the same time periods.

Migration of chlordane bound to soil particles may occur under surface runoff conditions. In studies addressing pesticide loadings to two major river basins (1534), it was determined that greater inputs were originating from urban sources than from agricultural sources; surface runoff was suggested as the source. Translocation of chlordane from treated corn fields was also shown to occur via surface runoff (1558).

In summary, the available data suggest that sorption of chlordane onto soils of moderate to high organic content is strong. Under natural conditions, there is little vertical or horizontal movement in soil although surface runoff may cause some migration.

48.2.1.3 Volatilization from Soils

Transport of chlordane vapors through the air-filled pores of unsaturated soils is not expected to be a major transport pathway; modeling results indicate that a very small fraction of the chlordane loading will be present in the soil-air phase. However, due to its moderate vapor pressure (1E-05 µm Hg), some volatilization may occur. The minor components of the technical chlordane mixture are expected to be more volatile than the trans- and cis-chlordane isomers discussed here (1536). Half-lives for the volatilization of chlordane from stirred aqueous solution have been reported to be approximately 30 hours (1548), while volatilization half-lives in natural waters are on the order of 6-12 weeks (10). Volatilization from soil is expected to be much slower.

Several authors (1510, 1536, 1511, 1546) have described the effect of soil moisture content on the volatilization of chlordane. Laboratory and field studies have shown that relatively small amounts of moisture applied to a previously dry surface layer result in a marked increase in volatilization. The results of field experiments indicate that, with adequate moisture, pesticides applied to the surface of soil initially volatilize at rates proportional to the vapor density of the pure chemical. If the soil remains moist, volatilization appears to be controlled by diffusion; the time required for the volatilization rate to decline to half the initial rate is similar for most pesticides and ranges from 6-9 hours (1510). When moisture on soil surfaces decreases to an amount approximately equal to one monomolecular layer, the effective vapor pressure of chlordane and thus its volatilization is greatly reduced

(above one to three molecular layers of absorbed water, soil moisture changes have less influence on volatilization).

Field studies using two different application rates for chlordane showed 27% and 52% losses due to volatilization from damp, silty, clay loam over one month; no losses were observed over one month for chlordane applied to semi-arid sandy loam (1546). Similarly, a 10-fold decrease in chlordane volatilization was observed in experimental studies when a damp soil sample was allowed to dry out and the water-saturated air stream was replaced by dry air (1536). Glotfelty et al. (1511) presented volatilization data for chlordane applied to the surface of a moist silt loam soil and a drier sandy loam. Fairly rapid volatilization of chlordane from the surface of the moist silt loam was observed (50% lost in 2.5 days). By contrast, losses from the surface of the sandy soil were much lower (2% lost after 50 hours) probably due to the lack of capillary wetting which created a dry soil surface; losses remained low until moisture was applied. Another study (1510) reported 50% volatilization from moist soil after 11 days. Several studies (1243, 1498) have documented the transport of soil-applied chlordane into the indoor air of residences. Most homes were slab-on-grade with sub-slab or intra-slab ventilation ducting. Vapor-phase transport or volatilization is the likely migration route.

Volatilization losses from environmental soils vary greatly with the extent of incorporation into the soil column and the manner of application. A comparative study of different chlordane formulations demonstrated that liquid formulations volatilize more easily than granular formulations (1535). In general, volatilization losses from environmental soils will be lower than those reported for experimental surface soils. However, heavy application to vegetation or other surfaces may yield extremely rapid volatilization and the persistence within the affected area may be on the order of days rather than the longer times required for dissipation after incorporation into soil.

48.2.2 Transformation Processes in Soil/Ground-water Systems

Chlordane has been reported to be susceptible to photolysis and biodegradation. Evidence for the photoisomerization of chlordane in the presence of photosensitizers has been summarized in References 10 and 806. In the presence of acetone, a thin film of technical chlordane exposed to sunlight was 85% degraded in 155 hours; under the same conditions, trans-chlordane was 60% degraded in 50 hours and cis-chlordane was 99% degraded in 27 hours (1549). The same authors reported that thin films of cis-chlordane exposed to sunlight for 460 hours exhibited 10% degradation. Rapid photolytic degradation of chlordane on bean leaves treated with rotenone (photochemical sensitizer) has been reported (1550); the authors observed 70 to 80% loss of cis-chlordane and 15 to 20% loss of trans-chlordane in four hours. No loss was observed in the absence of rotenone. No information regarding the environmental photolysis of chlordane in the presence of natural substances was available.

Evidence of the microbial degradation of chlordane has been presented by several authors (1551-1553). However, data on microbial degradation in soil environments are very limited. Slow degradation in soils has been reported in several studies (1554, 1555), and no significant degradation was reported in four soils over a three-month period under flooded and upland conditions (1556). Carter and Stringer (1557) reported that degradation was greater in the surface soil than in lower layers; 45% degradation in the upper 1-3 cm and 12.5% degradation in the lower layer was observed over 12 months. Another study examined degradation in sand, loam and clay soils; after 30 months, chlordane was reported to be 80-90% degraded in all systems (1547). The half-life for degradation of chlordane in natural soils is expected to be on the order of 2-4 years (1540).

48.2.3 Primary Routes of Exposure from Soil/Ground-water Systems

The above discussion of fate pathways suggests that chlordane is moderately volatile, is very strongly sorbed to soil, and has a high potential for bioaccumulation. These fate characteristics suggest several potential exposure pathways.

Volatilization of chlordane from a disposal site could result in inhalation exposure to workers or residents in the area under certain conditions as described in Section 48.2.2. The potential for ground water contamination is limited by the strong adsorptive characteristics of chlordane. However, the persistence of this chemical has allowed its transport to drinking water supplies. Mitre (83) reported that chlordane has been found at 7 of the 546 National Priority List (NPL) sites. It was detected at 5 sites in ground water, 4 sites in surface water, and 1 site in air. Chlordane has also been reported in ground water in the vicinity of houses treated for termite control. It has been detected in drinking water in five states. In New Jersey, five wells contained chlordane at 0.01 mg/L to 0.02 mg/L. One state reported chlordane in 49% of the 87 ground-water systems sampled (992). These data indicate that ground water contamination by chlordane can occur in some situations, even though it is strongly adsorbed to organic matter in soil.

The movement of chlordane in ground water or its movement with soil particles may result in discharge to surface water. As a result, ingestion exposures may occur resulting from the use of surface waters as drinking water supplies, and dermal exposures may result from the recreational use of surface waters. More importantly, however, is the potential for uptake of chlordane by aquatic organisms or domestic animals. The high bioconcentration factor and the persistence of chlordane suggest that these can be important exposure pathways from soil/ground-water systems.

Wood et al. (1545) reported the results of a study that suggested that fish contamination with chlordane in a Long Island, NY lake resulted from ground water discharges. The authors hypothesized that chlordane was passing through the sand-gravel substratum and accumulating in the lake sediment. Fish concentrations of 5.2 mg/g in carp fillets and 0.38 mg/g in bass fillets were found in this lake.

48.2.4 Other Sources of Human Exposure

Chlordane has been used as a pesticide in the United States for over 30 years for termite control, as an insecticide for homes and gardens, and as an insecticide for field crops. Although most uses of chlordane have now been cancelled, it is still commonly found in the environment.

Schafer et al. (1241) found that 20% of the 500 samples of finished drinking water from the Mississippi and Missouri River contained chlordane at concentrations up to 8 ppb. However, chlordane does not appear to be a common contaminant in drinking water nationwide. Data from the U.S. National Surface Water Monitoring Program show that chlordane has been detected in 1.1% of the surface water samples taken from 1976 to 1980, with a maximum value of 0.23 ppb. It was more commonly detected in the sediment (15.3%) up to a concentration of 2964 ppb (1242).

Similarly, air exposures to chlordane appear to be low (994). Carey and Kutz (1242) reported that 11.4% of 123 air samples at 10 U.S. locations contained chlordane. The mean concentration was 0.4 ng/m^3 and the maximum was 7.3 ng/m^3 Houses previously treated for termites may contain higher concentrations of chlordane in the air. Wright and Leidy (1243) found chlordane levels of 0.30 mg/m^3 in the air of homes before treatment, which was not readily explained. After treatment, concentrations up to about 5 mg/m^3 persisted to 12 months when sampling was discontinued. In addition, chlordane has been found in the air of slab houses that had been treated for termites below the slab. Livingston and Jones (1498) found that 77% of the apartments sampled that had been treated 2-16 years previously had detectable concentrations of chlordane up to 37.9 mg/m^3. Apartments that were sampled 1 year after treatment showed concentrations up to 263.5 mg/m^3. In further studies, Barnes (1500) found that houses treated prior to construction were much less likely to have detectable chlordane concentrations in the air (9% as compared to 74%). Again these houses were slab-on-grade with sub- or intra-lab ventilation ducting.

Food appears to be the most common source of human exposure to chlordane, although levels are generally low. Some crops are able to translocate chlordane from soil, where it is persistent, and it may concentrate in oils, meat, milk and eggs (994). Gartrell et al. (1244) reported dietary intakes of total chlordane as <0.001 to 0.01 mg/kg of body weight/day for infants during the years 1976 to 1979 and 0.0003 to 0.032 mg/kg/day for toddlers. Adult intakes ranged from 0.003-0.004 ug/kg/day over the same time period (1245). Dietary intake in Canada is similarly low. Over the period of 1976 - 1978, the average dietary intake was less than 0.001 mg/kg/day (1246).

48.3 HUMAN HEALTH CONSIDERATIONS

48.3.1 Animal Studies

48.3.1.1 Carcinogenicity

Chlordane produces dose-dependent incidence of liver neoplasms in mice following oral administration. Data concerning rats are inconclusive (25).

In an 80-week NCI study, B6C3F$_1$ mice were fed analytical-grade chlordane, consisting of 94.8% chlordane (71.7% cis; 23.1% trans), 0.3% heptachlor, 0.6% nonachlor, 1.1% hexachlorocyclopentadiene, 0.25% chlordene isomers and other chlorinated compounds. All surviving mice were killed at 90-91 weeks. Time-weighted average dietary concentrations were 29.9 and 56.2 ppm for males and 30.1 and 63.8 ppm for females. A dose-related increase in the incidence of hepatocellular carcinomas was found in males and females in the high-dose group - 87.8% and 69.3%, respectively, compared to 11% and 0% in matched controls (1302).

In contrast to the findings in mice, Osborne-Mendel rats, fed time-weighted average dietary concentrations of 203.5 or 407 ppm (males) and 120.8 or 241.5 ppm (females) did not show a significant incidence of hepatocellular carcinoma. In treated male rats, there was an excess of follicular-cell thyroid neoplasms and malignant fibrous histiocytomas but these were discounted because the rates of incidence were low (9-13%) and/or are known to be variable in control rat populations. In this study, the incidence of these neoplasms in control animals ranged from 3.4 to 7.8% (1302).

A dose-related incidence of hepatocytomegaly was observed in both male and female CD-1 mice administered 4, 25 or 50 ppm of technical chlordane in their diet for 18 months study (1303). A dose-related increase in the incidence of nodules or nodular hyperplasia of the liver was also reported (based on gross pathology) in males and females in the 25 and 50 ppm groups. There was an increased incidence of hepatomas in males at the 5 and 25 ppm levels, but this was not statistically significant. Interpretation of these results was complicated by a high mortality rate (27-86%) and the large number of tissues lost from autolysis. Subsequent reevaluations of the study by independent pathologists indicated that the majority of lesions diagnosed as nodular hyperplasia were more appropriately classified as hepatocellular carcinomas.

In a recent study, Williams and Numoto (1304) suggest that chlordane has the properties of a promoting agent. They found that groups of male B6C3F$_1$ mice exposed to 20 ppm of the carcinogen diethylnitrosamine (DEN) in drinking water for 14 weeks followed by 25 weeks of a 25 or 50 ppm chlordane diet each had an 81% incidence of liver neoplasms. This is in contrast to a 40% incidence in animals given only DEN for 14 weeks and a 10.7% incidence in untreated controls.

48.3.1.2 Genotoxicity

Simmon et al. (3653) exposed Salmonella to cis-chlordane, trans-chlordane and technical grade chlordane in desiccators and in the plate incorporation assay; only technical grade chlordane was found to be mutagenic in strains TA98, TA100 and TA 1535 with or without metabolic activation. Chlordane's genotoxicity may have been due to chemical impurities (996, 3653). Negative results were also observed by Mortelmans et al. (3469) in this assay using 99% pure chlordane and 20 minutes preincubation with or without rat or Syrian hamster liver as a source of metabolic activation.

Vigfusson et al. (3815) exposed mudminnows for 11 days to chlordane (43.2% pure) and observed significant increases in sister chromatid exchanges in the intestinal cells of the treated fish.

In mammalian systems, chlordane induced unscheduled DNA synthesis in SV-40 human fibroblasts without activation (997) but did not do so in cultured mouse, rat and hamster hepatocytes (25, 3575, 3431). Telang et al. (3704) did not observe any increase above controls in an HPRT assay in which adult rat liver cells were exposed to chlordane for 72 hrs. In a similar test, but using human foreskin fibroblasts treated for 24 hrs, Tong et al. (3722) did not observe any positive effects.

McGregor et al. (3439) found technical grade chlordane to be positive in inducing mutations at the thymidine kinase locus in cultured L5178Y mouse lymphoma cells tested without metabolic activation at a dose of 25 μg/ml for 4 hrs. Sobti et al. (3665) also found that chlordane induced sister chromatid exchanges at the lowest concentration tested with a frequency comparable with that of the positive control in human lymphoid cells treated for 1 hour in culture.

Negative results were obtained in dominant lethal assays in mice receiving either cis-chlordane (42, 58 or 290 mg/kg ip or 5 daily oral doses of 75 mg/kg) or trans-chlordane (5 daily oral doses of 50 mg/kg) (998). Similar negative results were reported in mice given oral or ip doses of 50 or 100 mg/kg technical-grade chlordane (999).

Available human data, however, are insufficient to permit an evaluation of the potential carcinogenicity of chlordane for humans at this time.

Results in mutagenicity tests including an in vivo assay are generally negative and do not indicate a mutagenic hazard.

48.3.1.3 Teratogenicity, Embryotoxicity and Reproductive Effects

Mice fed diets containing 100 mg/kg diet for 6 generations showed decreased viability in the first and second generations. In the third generation, no offspring were produced. At 50 mg/kg diet, viability was reduced in the fourth and fifth

generations and at 25 mg/kg diet, no statistically significant effects were observed after 6 generations (1000). Rats maintained from weaning on a diet containing a chlordane level of 320 mg/kg diet, showed reduced rates of mating and of viable litters and an increased rate in the death of progeny prior to weaning (1310). In a 3 generation study conducted in rats, dietary levels of up to 30 mg/kg did not have any effect on fertility, number of off-spring or the weight, growth or mortality rate of the animals to weaning age (1301). Arnold et al. (3037) found no dominant lethal changes in litters from untreated female mice which had been mated to males treated either by gavage or ip to 50 or 100 mg/kg of chlordane given in a single dose. Teratology test systems which evaluate postnatal growth and viability in the mouse (3119) observed no effect on these values in mice whose dams were treated by gavage with 50 mg/kg of chlordane on prenatal days 8 through 12. However, Gray et al. (3252) found transient hyperactivity in the offspring of the treated females during a maze activity test on postnatal day 22. Other than this transient hyperactivity, no evidence of teratogenicity was found in any study.

48.3.1.4 Other Toxicologic Effects

48.3.1.4.1 Short-term Toxicity

The signs associated with acute chlordane poisoning are ataxia, convulsions, respiratory failure and cyanosis. Pathological manifestations include hemorrhage in the gastrointestinal tract, liver, kidneys, lung and heart, pulmonary edema and congestion, and degenerative changes in the central nervous system (994).

The acute toxicities are difficult to interpret since they are dependent upon both the purity of the chlordane and the solvent used (2, 12). Chlordane manufactured before 1951 was more toxic than that manufactured during and after 1951. The greater toxicity of the early product was partly due to the presence of hexachlorocyclopentadiene (12). In 1952, Ingle (1305) reported an oral LD_{50} value of 250 mg/kg for rats. Later reports of LD_{50} values for the rat ranged from 283 to 590 mg/kg (1306, 1307). The cis- and trans-isomers have oral LD_{50} values of 392 and 327 mg/kg, respectively, while an equal mixture of both isomers resulted in an LD_{50} value of 371 mg/kg (1308).

Daily oral doses of 6.25 to 25 mg/kg administered in cottonseed oil for 15 days did not induce tremors or convulsions but daily doses of 50 mg/kg did induce toxic symptoms and death. Dose-related increases in cytoplasmic bodies were observed in the liver cells in all groups (1310).

The acute inhalation toxicity of chlordane was investigated in the early 1950's by Frings and O'Tousa (1312) and Ingle (1313). The former investigators exposed female mice to air saturated with chlordane for up to 4 days. The chlordane contained 25 to 40% unspecified related compounds. Most of the animals died within 4 days; the remainder died within the next 10 days. In contrast, Ingle exposed mice for 14 days and observed no deaths or adverse effects on the liver or central

nervous system. However, when hexachlorocylclopentadiene was added, toxic effects and fatalities were observed. Ingle speculated that the toxicity seen by Frings and O'Tousa may have been caused by chlordane contaminated with hexachlorocyclopentadiene.

Dermal LD_{50} values in rats ranged from 590 to 840 mg/kg (2); however, Ingle (1309) reported that more purified chlordane raised the LD_{50} value to 1100-1200 mg/kg. A dermal dose of less than 780 mg/kg of "early" (i.e., less purified) chlordane was reported to cause severe skin irritation, tremors and convulsions in rabbits (1314). A purer product was only half as toxic to rabbits as the earlier chlordane formulation and did not cause any skin irritation or damage to the mucous membranes (994). Evidence for testicular tissue degeneration in mice was provided by Balash et al. (3047). Two groups of mice receiving oral doses of 0.08 or 0.25 mg chlordane per day for 30 days exhibited degenerative changes of the spermatogenic epithelium when compared to corn oil controls. Seminiferous tubules were congested with necrotic cells and oedematous fluid, and the number of spermatocytes was reduced. The degenerative changes were dose-related.

48.3.1.4.2 Chronic Toxicity

Chronic chlordane poisoning in animals produces degenerative changes in the liver, renal tubules, lungs, heart and intestinal submucosa (17). Chlordane is slowly metabolized to oxychlordane which is more toxic than chlordane itself (oral LD_{50} (rat) 19.1 mg/kg) (994). The alpha (cis) isomer is retained primarily in body fat but also in the kidney, muscle, liver, and brain in decreasing quantities. The highest concentrations of the gamma (trans) isomer are found in the kidney, followed by fat, liver, muscle and brain. Oxychlordane is found primarily in fat but at higher concentrations than chlordane (12). Because of its storage in body fat, chlordane has a high degree of persistence and therefore a high potential for toxicity (17).

The Joint Meeting on Pesticide Residues has reviewed chronic oral toxicity data on chlordane and established the following no-observed adverse-effect-levels: in the rat, 5 mg/kg diet, equivalent to 0.25 mg/kg body weight; in the dog, 3 mg/kg diet, equivalent to 0.075 mg/kg body weight (1315).

Ingle (1316) in a two-year study, fed rats dietary levels of "early" technical chlordane ranging from 5 to 300 mg/kg. Convulsions and tremors were observed in animals receiving 150 mg/kg or more. Growth retardation and severe lung, liver and kidney damage were also observed at these levels. No lung or kidney damage was seen at the 5, 10 or 30 mg/kg levels. Liver damage was slight at 30 mg/kg, minimal at 10 mg/kg and absent at 5 mg/kg.

In a subsequent study on rats, technical chlordane containing fewer by-products was administered at levels of 2.5 to 300 mg/kg diet for 2 years. Cellular alterations were seen at 50 mg/kg and higher. Changes in food consumption, growth and mortality rate were seen only at the highest dose (1318).

In dogs fed dietary levels of 0.3 to 30 mg/kg for two years, no treatment-related changes were seen in behavior, food consumption, appearance, body weight, hematology or plasma biochemistry. Relative liver weights were increased and liver enzymes were altered at the 15 and 30 mg/kg levels (1317).

48.3.2 Human and Epidemiologic Studies

48.3.2.1 Short-term Toxicologic Effects

Acute chlordane poisoning produces CNS symptoms including headache, blurred vision, dizziness, slight involuntary muscle movements, tremor, sweating, insomnia, nausea and general malaise. More severe illness is characterized by muscular contractions and epileptiform convulsions, with loss of consciousness, urinary and fecal incontinence, disorientation, psychic disturbances and memory loss. These episodes may recur for 2 to 4 months following the cessation of exposure and are characterized by abnormal EEG patterns (995).

For adults, the estimated fatal oral dose is between 6 and 60 g, although convulsive symptoms have occurred with as little as 2.25 g (2, 17). Olanoff et al. (1319) reported a case in which an individual ingested 215 g of chlordane in a liquid pesticide formulation which had been stored in a wine bottle. The rapid induction of emesis probably prevented this individual's death. Symptoms included vomiting, diarrhea, seizures, coma and respiratory failure. Whole blood chlordane concentration 3.5 hours after ingestion was 5 mg/L. The individual recovered after 13 days. Tissue samples obtained 58 days after ingestion revealed 5 ppm of chlordane metabolites (oxychlordane, heptachlor epoxide and trans-nonachlor) in the abdominal fat. This is substantially higher than the 0.1 to 0.4 ppm measured in the subcutaneous fat of the general U.S. population. In another case, a person who ingested 6 g (104 mg/kg) in talc suffered burns of the mouth, severe gastritis, diffuse pneumonia, anuria, mania and convulsions. Death occurred after 9.5 days. Autopsy revealed severe necrotizing bronchopneumonia and degeneration of the renal tubules (1322).

Chlordane contamination of a public water system in Chattanooga, Tennessee resulted in symptoms of mild toxicity in 18% of the affected population. Chlordane concentrations in the tap water of the 42 houses that were affected ranged from 0.1 to 92,500 ppb. In 23 houses, the concentration exceeded 100 ppb and 11 of these had concentrations in excess of 1000 ppb. A survey of 71 affected residents revealed that 13 (18%) had symptoms compatible with mild chlordane poisoning. These included nausea, vomiting, abdominal pain, dizziness, blurred vision, headache or muscle dysfunction. None was hospitalized and all recovered within 48 hours after exposure with no apparent chronic sequelae (1321).

An inhalation exposure reported by Garrettson et al. (1320) is indicative of the persistance of chlordane. In this case, a woman was exposed to chlordane vapors

over a 3 day period after spraying 16 gallons of the diluted insecticide through her home. Three days after the start of spraying she experienced numbness in her arm and around her nose and mouth which lasted from 3 to 4 weeks. She also experienced nausea and vomiting which persisted for 3 weeks and anorexia which persisted for 6 months. Severe headaches with a frequency of 2 per week lasted for 4 months. One month after exposure, myoclonic jerks began to occur. The reason for this time delay could not be explained. Anorexia and malaise induced the woman to seek treatment about 4 months after symptoms began. At this time, serum heptachlor was 30 ng/mL and fat heptachlor was 20 μg/g. After one week of treatment, the serum level dropped to 4 ng/mL. Treatment was continued on an out-patient basis and the patient reported symptomatic improvement.

Skin absorption of chlordane is rapid (46). A worker who spilled a 25% suspension on his clothing (which was not removed) began having convulsions 40 minutes later and died shortly thereafter (1322).

Technical grade chlordane is said to be irritating to the skin and mucous membranes but this may be due to the presence of contaminants (38). Presumably this is not a problem with the recently manufactured product (12). Chlordane may persist for long periods on the skin of persons using it. In one study, hexane rinsings of the hands of a former pest-control operator contained chlordane 2 years after his last known exposure (1323).

48.3.2.2 Chronic Toxicologic Effects

Limited studies of long-term human exposure to chlordane have revealed no consistent or significant detrimental effects. There are anecdotal reports suggesting a correlation between chlordane exposure and the subsequent development of aplastic anemia, leukemia and neuroblastoma (1324). Five out of fourteen children with neuroblastoma were exposed either pre- or postnatally to chlordane. Only 2 of the 6 cases with anemia or leukemia were exposed to chlordane alone. The other cases were complicated by exposures to multiple chemicals. These case reports do not provide sufficient information to support a causal relationship. In a 1981 case-control study, Wang and Gruffenman (1326) found no association between blood dyscrasias and occupational exposure to chlordane. Wang and MacMahon (1327) studied a cohort of 1403 workers employed for 3 months or longer in the production of chlordane or heptachlor between 1946 and 1975. The data indicated an excess of lung cancer which was not considered statistically significant (12 observed vs. 9 expected); however, there was a statistically significant excess in deaths from cerebrovascular disease (17 observed vs. 9.3 expected). These deaths all occurred after termination of employment and were not related to duration of exposure. Ditraglia et al. (1325) studied a cohort of these same workers who had achieved 6 months employment prior to December 31, 1964. This date was selected to allow for a sufficient latency period. These investigators found a deficit in observed deaths due to all malignant neoplasms. A slight excess of stomach cancer was observed, which was not statistically significant. Other studies of long-term chlordane exposure have

not revealed any abnormalities in the liver, kidneys, skin, nervous system and blood-forming organs. Princi and Spurbeck (1328) found no adverse effects in 34 men engaged in the production of insecticides, including chlordane and exposed through skin contact and inhalation for 3 months. Vapor concentrations were as high as 10 mg/m³. In addition, no adverse effects were seen in 15 workers exposed to vapor levels of 0.0012 - 0.0017 mg/m³ for periods of 1 to 15 years (1329) or in 24 men exposed to unspecified levels for 2 months to 5 years (1330).

48.3.3 Levels of Concern

The USEPA (355) has specified an ambient water quality criterion of zero for chlordane, based on the induction of liver carcinoma in mice. In that attainment of a zero concentration level may be infeasible in some cases, the concentrations of chlordane in water calculated to result in incremental lifetime cancer risks of 1E-05, 1E-06, and 1E-07 from ingestion of both water and contaminated aquatic organisms were estimated to be 4.6, 0.46 and 0.046 ng/L, respectively. Risk estimates are expressed as a probability of cancer after a lifetime daily consumption of two liters of water and 6.5 g of fish that have bioaccumulated chlordane. Thus a risk of 1E-05 implies that a lifetime daily consumption of two liters of drinking water and 6.5 g of contaminated fish at the criterion level of 4.6 ng/L of chlordane would be expected to produce one excess case of cancer above the normal background incidence for every 100,000 people exposed. It should be emphasized that these extrapolations are based on a number of assumptions and should be taken as crude estimates of human risk at best.

IARC (803) lists chlordane in category 3 (cannot be classified as to its carcinogenicity to humans) in its weight-of-evidence ranking for carcinogens, and the USEPA (3742) lists chlordane in Group B2 (probable and human carcinogen).

The proposed MCLG is 0 µg/L and the proposed MCL is 2 µg/L in drinking water (3883). The WHO (666) recommends a level of 0.3 µg/L for chlordane (total isomers) in drinking water. A temporary FAO/WHO ADI for humans of 0 to 1 µg/kg body weight was confirmed by FAO in 1977 (666).

Both OSHA (298) and the ACGIH (3005) currently permit 8-hour time-weighted average exposures of 0.5 mg/m³ for chlordane, with a notation of possible skin absorption.

48.3.4 Hazard Assessment

Chlordane is moderately toxic in acute exposures. Acute lethal values generally fall in the 200 to 1000 mg/kg range (59). Bioaccumulation, primarily in body fat, may result from continuous exposure. In humans, chlordane primarily affects the central nervous system, inducing irritability, tremors and convulsions. The fatal oral dose for adults is estimated to be between 6 and 60 g, with onset of symptoms occurring

within 45 minutes to several hours after ingestion (2, 17). Chlordane is readily absorbed through the skin (46).

The carcinogenicity of chlordane has been studied in both mice and rats (1302). Inclusion of up to 407 ppm analytical-grade chlordane in the diet of rats did not induce hepatocellular carcinoma. In the mouse, up to 56 ppm analytical grade or 25 ppm technical-grade chlordane did induce a significant incidence of hepatocellular carcinoma. No significant carcinogenic effect was noted in mice fed 30 ppm analytical chlordane and no evidence of carcinoma was seen with 5 ppm technical chlordane. Thus, the carcinogenic activity noted at the 25 ppm level with technical chlordane may reflect the presence of heptachlor.

Considerable controversy exists concerning the interpretation of hepatic lesions observed in laboratory mice exposed to chlordane in the diet, especially with respect to the possible implications of these findings for man. In part, this situation arises from a lack of agreement among pathologists on diagnostic criteria for classifying hepatic lesions as benign or malignant neoplasia. Another factor is the high background incidence of these tumors in untreated mice.

Several epidemiologic studies involving occupational exposure to chlordane do not provide any evidence of increased cancer mortality (1325, 1326, 1327) although anecdotal reports suggest a relationship between exposure to chlordane and blood dyscrasias, acute leukemia and development of neuroblastomas in children (1324). Available human data, however, are insufficient to permit an evaluation of the potential carcinogenicity of chlordane for humans at this time.

Results in mutagenicity tests including an in vivo assay are generally negative and do not indicate a mutagenic hazard.

Little or no effect was seen in either mice or rats fed 25 and 30 mg/kg diet of chlordane over several generations. Higher doses resulted in decreased fertility and viability of offspring. No teratogenic effects were observed (1000, 1301, 1310).

Chronic animal studies suggest liver and kidney damage but these findings have not been observed with long-term human exposure.

48.4 SAMPLING AND ANALYSIS CONSIDERATIONS

Determination of chlordane concentrations in soil and water requires collection of a representative field sample and laboratory analysis. Care is required to prevent losses during sample collection and storage. Soil and water samples should be collected in glass containers; extraction of samples should be completed within 7 days of sampling and analysis completed within 40 days. In addition to the targeted samples, quality control samples such as field blanks, duplicates, and spiked matrices may be specified in the recommended methods.

EPA-approved procedures for the analysis of chlordane, one of the PEA priority pollutants, in aqueous samples include EPA Methods 608 625 (65), 8080, and 8250 (63). Prior to analysis, samples are extracted with methylene chloride as a solvent using a separatory funnel or a continuous liquid-liquid extractor. The concentrated sample extract is solvent exchanged into hexane and an aliquot of the hexane extract injected onto a gas chromatographic (GC) column using a solvent flush technique. The GC column is programmed to separate the semi-volatile organics; chlordane is then detected with an electron capture detector (Methods 608 and 8080) or a mass spectrometer (Methods 625 and 8250).

The EPA procedures recommended for chlordane analysis in soil and waste samples, Methods 8080 and 8250 (63), differ from the aqueous procedures primarily in the preparation of the sample extract. Solid samples are extracted with hexane/acetone using either soxhlet extraction or sonication methods. Neat and diluted organic liquids may be analyzed by direct injection.

It may be necessary to cleanup the sample extracts to remove impurities that interfere with the final analysis. Gel permeation chromatography (GPC) (Method 3640), column adsorption chromatography (Method 3620), or various techniques for removing sulfur (Method 3660) may be used in this case prior to GC/electron capture or GC/mass spectrometric analysis. Interferences from phthalates may be minimized by avoiding sample contact with all plastic materials. The microcoulometric and electrolytic conductivity detectors are more selective and will eliminate interferences from phthalate esters.

Typical chlordane detection limits that can be obtained in wastewaters and non-aqueous samples (wastes, soils, etc.) are shown below. The actual detection limit achieved in a given analysis will vary with instrument sensitivity and matrix effects. (Detection limits using Methods 625 and 8250 were not indicated; chlordane is a mixture of isomers.)

Aqueous Detection Limit	Non-Aqueous Detection Limit
0.014 µg/L (Method 608)	9 µg/kg (Method 8080)
0.14 µg/L (Method 8080)	

48.5 REFERENCES

Note: The nonsequential numbers of the references reflect the order of references as they appear in the master bibliography.

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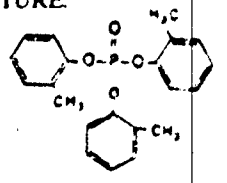
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COMMON SYNONYMS:	CAS REG.NO.: 78-30-8 FORMULA: $C_{21}H_{21}O_4P$ NIOSH NO: TD0350000 STRUCTURE: 	AIR W/V CONVERSION FACTOR at 25°C (12) 15.04 mg/m³ ≈ 1 ppm; 0.0665 ppm ≈ 1 mg/m³ MOLECULAR WEIGHT: 368.37
Phosphonic acid, tris (2-methyl-phenyl) ester TOCP TOTP Tri-o-cresyl phosphate Tri-o-tolyl phosphate		

REACTIVITY	Given its chemical structure, TOCP is likely to be considered in the reactivity group of organophosphates, phosphothioates, and phosphodithioates for compatibility classification purposes. Such substances typically generate heat in reactions with alkali or alkaline earth elemental metals; heat and toxic gases in reactions with mineral acids; and heat and possible explosion with caustics. Additionally reported reactions are unknown but possibly hazardous reactions with azo or diazo compounds, hydrazines or organic peroxides or hydroperoxides. One specific source notes that TOCP can react with oxidizing agents. Another, however, states that TOCP has no hazardous incompatibilities (51, 54, 511).

PHYSICO-CHEMICAL DATA	• Physical State: Liquid (at 20°C)	(23)
	• Color: Practically colorless	(23)
	• Odor: No data	
	• Odor Threshold: No data	
	• Density: 1.1955 g/ml (at 20°C)	(68)
	• Freeze/Melt Point: -33.00, 11.00°C	(60,68)
	• Boiling Point: 410.00°C	(68)
	• Flash Point: 225.00°C	(12,506)
	• Flammable Limits: No data	(506)
	• Autoignition Temp.: 385.0°C	(506)

PHYSICO-CHEMICAL DATA (Cont.)	• Vapor Pressure: 1.00E-07 mm Hg (at 20°C) (1219) • Satd. Conc. in Air: 2.0000E-03 mg/m^3 (at 20°C) (1219) • Solubility in Water: 3.00E-01 mg/L (at 20°C) (38) • Viscosity: 102.200 cp (at 21°C) (60) • Surface Tension: 4.4000E+01 dyne/cm (at 25°C) (60) • Log (Octanol-Water Partition Coeff.): 5.11 (29) • Soil Adsorp. Coeff.: 6.20E+04 (611) • Henry's Law Const.: 1.30E-07 $atm \cdot m^3/mol$ (at 20°C) (964) • Bioconc. Factor: 1.70E+02 (fathead minnow) (806)
PERSISTENCE IN THE SOIL-WATER SYSTEM	Fairly immobile in soil water systems due to strong soil sorption, low water solubility and low vapor pressure. Resistant to photolysis and hydrolysis but easily biodegraded.
PATHWAYS OF EXPOSURE	The primary pathway from soil/ground-water systems is the migration of TOCP to ground water drinking water supplies, although it is expected to be relatively immobile. Bioaccumulation by aquatic organisms or domestic animals may be important exposure pathways in some instances. Inhalation is not expected to be a significant exposure route.

HEALTH HAZARD DATA	Signs and Symptoms of Short-term Human Exposure: (54) The major effects of TOCP are on the spinal cord and peripheral nervous system. After acute exposure, nausea, vomiting, diarrhea and abdominal pain are seen followed by a latent period of 3 to 30 days. Next, muscle soreness and numbness of fingers, calf muscles, and toes occur, progressing to foot and wrist drop. These effects can be manifested after ingestion, inhalation or dermal absorption of TOCP. Acute Toxicity Studies: ORAL: LD_{Lo} 1160 mg/kg — Rat (47) LD_{Lo} 1000 mg/kg — Human(59) SKIN: LD_{50} 1500 mg/kg — Cat (1352) Long-Term Effects: Peripheral neuropathy, paralysis of lower arms and legs Pregnancy/Neonate Data: Testicular toxicity in rats Genotoxicity Data: Limited data are negative Carcinogenicity Classification: IARC - No data NTP - No data EPA - No data
HANDLING PRECAUTIONS	Handle only with adequate ventilation • Vapor levels of 0.1-0.5 mg/m³: any dust or mist respirator except single use • 0.5-1.0 mg/m³: any supplied-air respirator, self- contained breathing apparatus, fume respirator, high efficiency particulate filter respirator or dust and mist respirator, except single-use or quarter mask • Chemical goggles if there is probability of eye contact • Protective clothing and gloves to prevent repeated or prolonged contact with the liquid.

ENVIRONMENTAL AND OCCUPATIONAL STANDARDS AND CRITERIA

AIR EXPOSURE LIMITS:

Standards
- OSHA TWA (8-hr): 0.1 mg/m³ (skin)
- AFOSH PEL (8-hr TWA): 0.1 mg/m³ (skin); STEL (15-min): 0.3 mg/m³

Criteria
- NIOSH IDLH (30-min): 40 mg/m³
- NIOSH REL: None established
- ACGIH TLV® (8-hr TWA): 0.1 mg/m³ (skin)
- ACGIH STEL (15-min): Deleted

WATER EXPOSURE LIMITS:

Drinking Water Standards
None established

EPA Health Advisories and Cancer Risk Levels
None established

WHO Drinking Water Guideline
No information available.

EPA Ambient Water Quality Criteria
- Human Health (355)
  - No criterion established; tri-o-cresyl phosphate is not a priority pollutant.
- Aquatic Life (355)
  - No criterion established; tri-o-cresyl phosphate is not a priority pollutant.

REFERENCE DOSES:

No reference dose available.

REGULATORY STATUS (as of 01-MAR-89)

Promulgated Regulations

- Federal Programs

  Toxic Substances Control Act (TSCA)
  Manufacturers, processors or distributors of tri-o-cresyl phosphate must report production, usage and disposal information to EPA. They, as well as others who possess health and safety studies on tri-o-cresyl phosphate, must submit them to EPA (334, 3789).

  Marine Protection Research and Sanctuaries Act (MPRSA)
  Ocean dumping of organohalogen compounds as well as the dumping of known or suspected carcinogens, mutagens or teratogens is prohibited except when they are present as trace contaminants. Permit applicants are exempt from these regulations if they can demonstrate that such chemical constituents are non-toxic and non-bioaccumulative in the marine environment or are rapidly rendered harmless by physical, chemical or biological processes in the sea (309).

  Occupational Safety and Health Act (OSHA)
  Employee exposure to tri-o-cresyl phosphate shall not exceed an 8-hour time-weighted average (TWA) of 0.1 mg/m^3. Employee skin exposure to tri-o-cresyl phosphate shall be prevented/reduced through the use of protective clothing and practices (3539).

- State Water Programs

  Although all states have adopted EPA Ambient Water Quality Criteria nd NPDWRs as their promulgated state regulations, either by narrative reference or by relisting the specific numeric criteria, numeric criteria have not been set for this chemical under the CWA or NPDWRs (see Water Exposure Limits section). There are no state water regulations specific to this chemical.

Proposed Regulations

- Federal Programs

  No proposed regulations are pending.

- State Water Programs

  No proposed regulations are pending.

  MOST STATES
  Most states are in the process of revising their water programs and proposing changes to their regulations which will follow EPA's regulations when they become final. Contact with state officers is advised. Changes are projected for 1989-90 (3683).

EEC Directives

Directive Relating to the Quality of Water for Human Consumption (540)
The maximum admissible concentration for tri-o-cresyl phosphate is 0.1 μg/L. The total maximum admissible concentration for pesticides and related products is 0.5 μg/L.

Directive on Ground-Water (538)
Direct discharge into ground-water (i.e., without percolation through the ground or subsoil) of organophosphorous compounds, organohalogen compounds and substances which may form such compounds in the aquatic environment, substances which possess carcinogenic, mutagenic or teratogenic properties in or via the aquatic environment and mineral oils and hydrocarbons is prohibited. Appropriate measures deemed necessary to prevent indirect discharge into ground-water (i.e., via percolation through ground or subsoil) of these substances shall be taken by member countries.

Directive on the Discharge of Dangerous Substances (535)
Organohalogens, organophosphates, petroleum hydrocarbons, carcinogens or substances which have a deleterious effect on the taste and/or odor of human food derived from aquatic environments cannot be discharged into inland surface waters, territorial waters or internal coastal waters without prior authorization from member countries which issue emission standards. A system of zero- emission applies to discharge of these substances into ground-water.

Directive on Marketing and Use of Dangerous Substances (541)
Tri-o-cresyl phosphate may not be used in ornamental objects intended to produce light or color effects by means of different phases.

Directive on the Classification, Packaging and Labeling of Dangerous Substances (787)
Tri-o-cresyl phosphate is classified as toxic substance and is subject to packaging and labeling regulations.

Directive on Paints, Varnishes, Printing Inks, Adhesives and Similar Products (1334)
Tri-o-cresyl phosphate mixtures containing more than 1% esterified o-cresol are classified as toxic substances when present at concentrations greater than 1% nd as harmful substances when present at concentrations ranging from 0.2 to 1%. Mixtures containing a maximum of 1% esterified o-cresol are classified as harmful substances when present at concentrations equal to or greater than 5%.

Directive on the Approximation of the Laws, Regulations and Administrative Provisions Relating to the Classification, Packaging and Labeling of Dangerous Preparations (3991)
The labels on packages containing preparations calssified as very toxic, toxic or corrosive must bear the safety advise S1/S2 and 346 in addition to the specific safety advice. If it is physically impossible to give such information, the package must be accompanied by precise and easily understood instructions.

EEC Directives - Proposed
Resolution on a List of Second-Category Pollutants (545)
Tri-o-cresyl phosphate is one of the second-category pollutants to be studied by the Commision in the programme of action of the European Communities on Environment in order to reduce pollution and nuisances in the air and water. Risk to human health and the environment, and determination of quality standards to be applied will be assessed.

Council of European Communities Proposal on the Dumping of Waste at Sea Comm(85) 373 Final
EEC has proposed that the dumping of organohalogen compounds at sea be prohibited. EEC has proposed that the dumping of pesticides at sea be forbidden without prior issue of a special permit. Dumping areas shall be designated in the permit.

49.1 MAJOR USES

Tricresyl phosphate exists in three isomeric forms, the ortho-, meta- and para-isomers. Tri-ortho-cresyl phosphate (TOCP), a component in commercial tricresyl phosphate, is the most toxic of the three isomers and is the only isomer of toxicologic importance. Modern mixtures contain less than 1% of the ortho isomer, although earlier formulations may have contained as much as 20% (17, 54). Tricresyl phosphate is used as a plasticizer for chlorinated rubber, vinyl plastics, polystyrene, polyacrylic and polymethacrylic esters, as a solvent and binder in nitrocellulose and various natural resins, as an adjuvant in the milling of pigment pastes and as an additive to synthetic lubricants and gasoline. It is also used as a hydraulic fluid, a fire retardant, and in phenol recovery from coke oven waste waters (54).

49.2 ENVIRONMENTAL FATE AND EXPOSURE PATHWAYS

49.2.1 Transport in Soil/Ground-water Systems

49.2.1.1 Overview

Although U.S. production and use of tricresyl phosphate has been heavy in the past (30-40 million pounds per year in the period from 1964 to 1973 (1491)), there is relatively little information available on its fate and transport in the environment. Based on available information, TOCP is expected to be relatively immobile in the soil/ground-water environment when present at low concentrations (dissolved in water). However, bulk quantities of the liquid chemical (e.g., from a spill) could be transported down through the unsaturated zone. TOCP is expected to sorb strongly onto soils, especially those with significant organic carbon content. Although the chemical is susceptible to biodegradation, it appears to be resistant to degradation by hydrolysis or photolysis so that it may persist for long periods in the soil/ground-water environment.

Environmental transport pathways for TOCP can be generally assessed by using an equilibrium partitioning model as shown in Table 49-1. These calculations predict the partitioning of low soil concentrations of the chemical among soil particles, soil water and soil air. The estimates for the unsaturated topsoil model show that essentially all of the chemical (99.99%) is sorbed to the soil, and only a very small amount (0.008%) is in solution and available for downward percolation. The model predicts negligible amounts to be present in the soil air phase and thus volatilization losses should be negligible. In saturated deep soils (containing no air and negligible soil organic carbon), the model predicts that most of the chemical (99.6%) will be sorbed and only a small amount (0.4%) present in the mobile ground-water phase.

TABLE 49-1
EQUILIBRIUM PARTITIONING CALCULATIONS FOR TRI-O-CRESYL PHOSPHATE IN MODEL ENVIRONMENTS[a]

Soil Environment	Estimated Percent of Total Mass of Chemical in Each Compartment		
	Soil	Soil-Water	Soil-Air
Unsaturated topsoil at[b,c] 20°C	99.99	0.008	1.4E-07
Saturated[d] deep soil	99.6	0.4	-

a) Calculations based on Mackay's equilibrium partitioning model (34, 35, 36); see Introduction in Volume 1 for description of model and environmental conditions chosen to represent an unsaturated topsoil and saturated deep soil. Calculated percentages should be considered as rough estimates and used only for general guidance.
b) Utilized estimated soil sorption coefficient: K_{oc} = 62,000 (611).
c) Henry's law constant taken as 1.3E-07 atm · m^3/mol at 20°C (964).
d) Used sorption coefficient $K_p = 0.001 \times K_{oc}$.

49.2.1.2 Sorption on Soils

A soil sorption constant (K_{oc}) of 62,000 has been estimated (611) based upon a measured value of the octanol-water partition coefficient (log K_{ow} = 5.11 (29)). This value of K_{oc} is indicative of relatively strong sorption to soils containing >0.1% organic carbon. The extent of sorption will increase with increasing soil organic carbon content. No data were found on the sorption of TOCP to soils and sediments.

49.2.1.3 Volatilization from Soils

Based upon an estimated vapor pressure of 1E-07 um Hg (20°C) (1219) and a Henry's law constant of 1.3E-07 atm · m^3/mol (20°C) (964), volatilization from soil is expected to be an unimportant transport pathway except for near-surface dry soils.

49.2.2 Transformation Processes in Soil/Ground-water Systems

TOCP is expected to be resistant to direct photolysis based on the fact that there is no light absorption above 290 nm (806). It is known that organophosphate chemicals can undergo hydrolysis, and that the reaction may be base-catalyzed (529, 806, 1493, 1494, 1495). However, the rate of hydrolysis in the environment is expected to be slow. One estimate gives the environmental hydrolysis half-life as 82 years at pH 7 and 30 days at pH 10 (806). The base-catalyzed reaction presumably results in initial cleavage of a phosphorus-oxygen bond (1491).

A variety of data is available on the biodegradability of tri-p-cresyl phosphate (CAS No. 78-32-0) and the isomer mixture tricresyl phosphate (CAS No. 1330-78-5), as well as TOCP (806, 1490, 1496, 1497). Most of these data show that tricresyl phosphates are significantly biodegraded by natural microorganisms obtained from sewage treatment plants and surface waters. Substantial or complete degradation took place within a few days in most tests. Examples of data from two tests using river and lake water are shown in Figures 49-1 and 49-2. In both cases, the

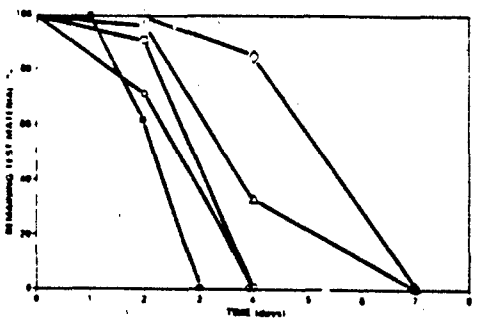


FIGURE 49-1

BIODEGRADATION OF TRICRESYL PHOSPHATE IN MISSISSIPPI RIVER WATER

Source: Saeger et al. (1490)

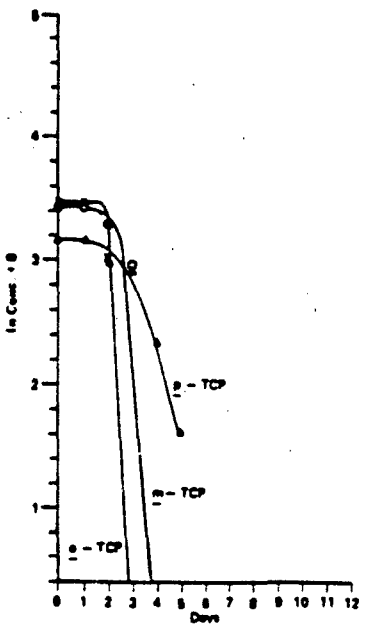


FIGURE 49-2

LOSS OF TRICRESYL PHOSPHATE ISOMERS IN LAKE ONTARIO WATER

Source: Howard and Deo (1496)

disappearance of the chemical represents primary biodegradation. One initial metabolite of tri-p-cresyl phosphate is reported to be p-hydroxybenzoic acid (806). Based on CO_2 evolution studies for tricresyl phosphate (isomer mixture), Saeger et al. (1490) conclude that the chemical undergoes ultimate biodegradation (in which all carbon is converted to CO_2) fairly easily. In their test using acclimated bacterial seed, 79% of the ultimate CO_2 production was reached after 7 days, 82% after 28 days, and 86% after 48 days.

49.2.3 Primary Routes of Exposure from Soil/Ground-water Systems

The above discussion of fate pathways suggests that TOCP is of low volatility, is strongly sorbed to soil, and has a moderate potential for bioaccumulation. These fate characteristics provide some indication of potentially important exposure pathways. Volatilization of TOCP from a disposal site is not likely to represent an important exposure pathway. The potential for ground-water contamination is limited by the strong adsorptive characteristics of TOCP. The presence of this compound in ground-water drinking water supplies has not been reported in the literature. As TOCP is expected to be relatively immobile in the soil/ground-water environment, discharges to surface water via this route are not expected to be significant. Any releases to surface water would be strongly sorbed to sediment and would not be likely to result in direct human exposure through drinking water. Uptake by aquatic organisms is possible, however, based on this compound's potential for bioaccumulation.

49.2.4 Other Sources of Human Exposure

The production of TOCP has declined dramatically in the last ten years. The primary source of exposure to this compound still appears to be in occupational settings (1788). To the extent that this compound is used in consumer products, direct consumer exposure is possible. However, environmental exposures to TOCP (through food, drinking water, and air) have not been reported (1788).

49.3 HUMAN HEALTH CONSIDERATIONS

49.3.1 Animal Studies

49.3.1.1 Carcinogenicity

No carcinogenicity data are available for TOCP. The NTP status report for Feb 8, 1989 indicates that tricresyl phosphate (CAS RN 1330-78-5) is a REF No. 8 chemical or "two-year studies: histopathology in progress."

49.3.1.2 Genotoxicity

No mutagenicity studies were found for TOCP. Haworth et al. (3276) tested tricresyl phosphate (no isomer specified) and the m-isomer in the Salmonella/ microsome assay and observed no significant increase in histidine revertants with or without metabolic activation. Tricresyl phosphate was also negative in the in vivo/in vitro unscheduled DNA synthesis assay as conducted by Mirsalis et al. (3454).

49.3.1.3 Teratogenicity, Embryotoxicity and Reproductive Effects

The testicular toxicity of TOCP was evaluated in F344 rats by Somkuti et al. (3669, 3670). Animals dosed orally with 10-150 mg/kg/day TOCP for 3-63 days had a time-dependent increase in the inhibition of sperm motility and an inhibition of testicular non-specific esterase. Pair-fed controls showed no signs of testicular toxicity (3670). Morphological testicular changes were evaluated by the same investigators after administering 150 mg/kg/day TOCP in corn oil for 3, 5, 7, 10, 14 or 21 days. A corn oil-treated group served as controls. By day 5 there were numerous detached spermatids. There was also a progressive decrease in sperm density in the seminiferous tubules (0 by day 14). Morphological findings indicate a possible selective effect of TOCP on the Sertoli cells (3669). Tocco et al. (3720) evaluated the teratogenic effect of tri-ortho-cresyl phosphate in rats treated with 87.5, 175, or 350 mg/kg/day from gestation days 6 through 18. The highest dose was lethal to 5 of 18 dams; however, no maternal toxicity was observed in the 87.5 or 175 mg/kg dose groups. No significant differences were noted among the treated and control groups for preimplantation losses or resorption rates. Malformation rates in all groups were too low to warrant statistical analysis. Fetal weights in the TOCP treated groups were significantly greater than in the control group; however, no differences among the treated groups were observed. This study indicates that TOCP is neither teratogenic nor fetotoxic in rats.

49.3.1.4 Other Toxicologic Effects

49.3.1.4.1 Short-term Toxicity

TOCP is a delayed onset neurotoxin which lacks the potent anticholinesterase properties exhibited by other organophosphorus compounds (200). Cats and chickens are the species most sensitive to the neurotoxic effects of TOCP and exhibit clinical and histopathological manifestations similar to humans. Rats and mice are less sensitive, apparently due to differences in pharmacokinetics and metabolism (1228). Species sensitivity also appears to be age-related with younger animals being more resistant to the toxic effects of TOCP (1227). In TOCP-treated cats and chickens, extensive damage is observed in the spinal cord and sciatic nerves. Damage to the myelin sheath and Schwann cells is secondary to the lesions in the axon, which start at the distal end of the longer axons (46). Cholinergic signs appear up to 2 days after dosing and may persist for several days until weakness and ataxia develop in the

lower limbs. This progresses to paralysis which, in severe cases, also affects the upper limbs (1227). This delayed polyneuropathy is known as organophosphorus-induced delayed neurotoxicity (OPIDN). It should be noted that OPIDN is not induced by all organophosphorus compounds. The ability of one compound but not another to cause OPIDN has not been fully elucidated (1348, 1227, 1228). Johnson (1227) has hypothesized that this process is initiated by phosphorylation of a protein neurotoxic esterase (NTE) in the nervous system. This phosphoryl-enzyme complex mus then undergo "aging", a process which involves loss of a group attached to the phosphorus, resulting in attachment of a negatively charged phosphoryl group to the protein. For compounds that age, if threshold levels of NTE inhibition are achieved, OPIDN occurs. The attainment of high levels of NTE inhibition (70-80%) in the brain, spinal cord or peripheral nerve tissue of experimental animals soon after dosing with an organophosphorus compound predicts the onset of clinical signs approximately two weeks later (1227, 1348). Support for the NTE hypothesis comes from the correlation between the inhibitory effect of many organophosphorus compounds on NTE and their ability to produce delayed neurotoxicity in hens. For example, TOCP, a known inducer of OPIDN, produces about 90% inhibition of NTE and 10% inhibition of acetylcholinesterase (AChE) in the hen brain. Parathion, another organophosphorus compound, does not induce OPIDN, has no significant effect on brain NTE activity, but does inhibit AChE activity upwards of 80% (1434). However, this correlation between high levels (>70%) of NTE inhibition and development of OPIDN has not been consistently observed (1228). Several dimethyl phosphates produce a high level of NTE inhibition in hens but do not cause OPIDN (1229). Conversely, Olajos et al. (1230) have found that hens developed OPIDN with only a 32% level of NTE inhibition after being given cumulative doses of 2-5 mg/kg diisopropyl phosphorofluoridate, another delayed onset neurotoxin. In rats, oral LD_{50} values for TOCP range from 1160 to 3000 mg/kg (47, 59). In cats, dermal and oral LD_{50} values were determined to be 1500 and 3000 mg/kg, respectively (1352). Chickens given oral doses of 100 mg/kg TOCP for 15 days had a 98% inhibition of NTE activity and experienced severe neurotoxic effects (1349). One oral dose of 750 mg/kg resulted in unsteady gait and ataxia within 21 days. In this case, NTE was inhibited by 87% (1350). On the other hand, CD-1 mice receiving 262 mg/kg by gavage for 30 days exhibited no signs of clinical neuropathy (1349) but rats given single oral doses of 3480 mg/kg had 90% NTE inhibition within 20 hours. They developed the neuropathology of OPIDN with severe central and peripheral nerve degeneration but remained resistant to ataxia (1351). In an unspecified species and route, 20-30 daily doses of 5 mg/kg TOCP were equivalent to a single dose of 120-200 mg/kg (1232). Single dermal doses of 250-2000 mg/kg produce delayed neurotoxic effects in cats, the severity of which were dose-dependent. Animals treated with 1000-2000 mg/kg developed severe cholinergic effects despite treatment with drugs to prevent these effects such as atropine and pralidoxime immediately after dosing (1353). Among the cholinergic effects seen were vomiting, diarrhea and anorexia. Neurological effects included leg weakness, difficulty in standing and muscle fasciculation. Cats treated with 2000 mg/kg dermally died within 25 days. Extensive axonal degeneration was seen in all cats treated with 1000 or 1500 mg/kg. Two out of three cats given a 500 mg/kg dermal application and all three animals

treated with 250 mg/kg showed histologic lesions indicative of OPIDN but did not exhibit any signs of toxicity. A single dermal dose of 100 mg/kg did not produce neurotoxicity in cats (1353).

49.3.1.4.2 Chronic Toxicity

Long-term administration of TOCP causes the same neurotoxic effects as acute administration provided that a threshold level of inhibition-aging of NTE is reached which triggers OPIDN. These threshold levels may be species-specific (1234). In mice, daily oral dosing of 225 mg/kg for 270 days caused a decrease in body weight gain, muscle wasting, weakness and ataxia which progressed to severe hind limb paralysis. No cholinergic signs of toxicity were present even though acetylcholinesterase was inhibited 65%. Neurotoxic esterase was inhibited by 87%. Histologic examination revealed extensive degeneration of the axon and myelin of the spinal cord (1234). Abou-Donia et al. (1353) examined the effect of long-term dermal application of 0.5-100 mg/kg to cats. The animals were treated for 90 days and observed for 30 days thereafter. Animals given 0.5 mg/kg did not show any signs of acute poisoning. Doses of 5-100 mg/kg produced signs of an acute effect; the onset, duration and severity of this effect were dose-dependent. Animals given 100 mg/kg had the most severe response which began 9 days after the first administration. They developed severe ataxia which progressed to paresis. All succumbed after a mean of 36 daily doses. Animals given 10 mg/kg developed acute poisoning after an average of 23 days. All developed severe ataxia and 1 of the 4 progressed to paresis. Cats given 5 mg/kg showed less severe acute effects (mild ataxia) after an average of 35 days. Cats given 1 mg/kg showed leg weakness after a mean of 74 doses. Histopathological changes in the spinal cord were seen in 2 of 3 cats given 100 mg/kg and in 5 of 6 given 10 mg/kg. Only 1 of 3 at the 5 mg/kg level had any spinal cord lesions. Spinal cords of those receiving 0.5 or 1 mg/kg were normal. A significant finding was that all surviving animals showed clinical improvement after TOCP was discontinued.

49.3.2 Human and Epidemiologic Studies

49.3.2.1 Short-term Toxicologic Effects

Most human intoxications with TOCP have involved accidental ingestion of adulterated alcoholic beverages and cooking oils (12). Fatalities are rare and occur primarily in individuals who have ingested large quantities in a short time. The lethal oral dose of TOCP for humans is about 1 g/kg; severe paralysis has resulted from ingestion of 6-7 mg/kg (46). In each episode of TOCP-poisoning, the clinical picture has been consistent. Shortly after ingestion there may be nausea, vomiting, diarrhea and abdominal pain lasting from a few hours to 2 days depending on the quantity ingested. After a latent period of 5 to 28 days, sharp cramplike pains may occur in the calves with some numbness in the hands and feet. Within a few hours, there is increasing weakness of the legs and feet which may progress to bilateral foot drop. A few days later, weakness of the fingers and wrists may develop, but the paralysis is

not usually as severe as that in the feet and legs. Sensory changes, if they occur, are minor. Muscular weakness may increase over a period of several weeks or months. Recovery may take months or years and in 25-30% of the cases, permanent residual effects remain in the lower limbs. In milder cases, recovery appears to be complete but there may be minor, residual neurologic effects (12, 46, 200). The most famous occurrence of TOCP poisoning was the "Jamaica ginger paralysis" which affected 50,000 Americans during the 1930's. "Jake", an ethanolic extract of ginger, was popular as tonic, particularly in the southern United States. The formula had originally contained castor oil but TOCP was substituted because of its lower cost. This led to an epidemic of partial paralysis among consumers of the beverage (1340). In a 47-year follow-up of eleven patients, 10 were found to be disabled (1343). Another epidemic poisoning occurred in Morocco in 1959. It involved 10,000 people who ingested olive oil adulterated with jet engine lubricating oil containing 3% TOCP. Ten to fifteen percent of those affected remained permanently disabled (1341). In 1977, an outbreak of acute polyneuropathy affected 20 young women in Sri Lanka who consumed gingili oil contaminated with TOCP over a two-week period. The total amount of TOCP ingested was estimated to be 2.8-5.6 g (70-140 mg/kg for a 40-kg female). Symptoms began with pain in the calves followed by weakness of feet and hands over a 1 to 3 day period. They had the characteristic high-stepping gait caused by bilateral foot drop. Other abnormal signs were wrist drop, bilateral claw hands and absent ankle jerks (1342). TOCP is not a skin irritant. About 0.1 to 0.4% of a dose applied to human skin is absorbed (12). Optic neuritis has been observed in cases of TOCP poisoning, but a link to TOCP as the causative agent has not been firmly established (19).

49.3.2.2 Chronic Toxicologic Effects

Little is known about the effects of chronic human exposure to low concentrations of TOCP. There have been only a few reports of occupational exposures (2). A case of permanent paralysis was reported in a man engaged in the manufacture of the meta and para isomers of tricresyl phosphate. As much as 6-10% TOCP was present as a contaminant during manufacture. The man had worked for 5 months before symptoms of anorexia, nausea and leg pain had developed (59). Hunter et al. (1344) described cases of polyneuritis in workers manufacturing various aryl phosphates with the suspicion that TOCP was the causative factor. Vapor concentrations ranged from 0.55-2.5 mg/m^3, however, absorption through the skin was not ruled out. Length of exposure was not reported. Inhibition of butyryl cholinesterase was reported in another group of workers engaged in the manufacture of aryl phosphates containing up to 20% TOCP. Vapor concentration of aryl phosphates ranged from 0.2 to 3 3.4 mg/m^3. No correlation was seen between the cholinesterase level and the degree of exposure or with minor gastrointestinal or neuromuscular symptoms. Length of exposure was not given (1345, 1346). A correlation between long-term TOCP exposure and chronic granulocytic leukemia was suggested by Duhrsen et al. (1347). The patient was an automobile mechanic who had worked with fuels, motor oil and lubricants for 32 years. Investigation revealed a tri-cresyl phosphate concentration of 0.6% in some of these products with 1-3% being

the ortho isomer. The patient had initially been examined for chronic polyneuropathy, beginning spastic paraparesis and leuko- and thrombocytosis of unknown origin. A diagnosis of chronic granulocytic anemia was made. No medical history or follow-up information was reported.

49.3.3 Levels of Concern

No criteria or standards have been established in the U.S. for TOCP with regard to acceptable levels of exposure via drinking water. EEC countries require a maximum TOCP concentration of 0.1 μg/L for water used for human consumption (540). Both OSHA (3539) and ACGIH (3005) have set an occupational exposure limit of 0.1 mg/m^3 for TOCP, with an indication of potential skin absorption. The TLV® was set to prevent neurotoxic effects (3005).

49.3.4 Hazard Assessment

Tricresyl phosphate exists in three isomeric forms: ortho-, meta- and para-isomers. Only the ortho form (i.e., TOCP) is of toxicologic importance. TOCP is moderately toxic via ingestion exposure and is readily absorbed through the skin without inducing local irritant effects; the oral and dermal LD_{50} values for the rat are 1160 and 300 mg/kg, respectively (47, 1352). The lethal dose for human is about 1 g/kg body weight (46). The major concern associated with TOCP exposure is a condition known as organophosphorus-induced delayed neurotoxicity (OPIDN). OPIDN has been observed in humans exposed to TOCP-adulterated food as well as experimentally in sensitive animal species. After a latent period of 3 to 30 days post-exposure, clinical signs of ataxia followed by paralysis of the lower extremities are exhibited. Neuronal lesions are characterized by degeneration of axons. Severe paralysis has resulted in humans from ingestion of 6 to 7 mg/kg (46). Recovery may take months to years; approximately 25-30% of the cases never recover. There are no data presently available with regard to the carcinogenic and mutagenic potential of TOCP. Tricresyl phosphate was found to be negative in the Salmonella/Ames test and in an in vivo study in which male rats were treated and their hepatocytes examined in an unscheduled DNA synthesis assay. Recent reports, however, have noted possible testicular toxicity in rats dosed with 10 to 150 mg/kg/day orally for periods ranging from 3 to 63 days (1338, 1339). The lack of data with respect to chronic human exposure to TOCP, carcinogenicity and mutagenicity when considered along with possible testicular toxicity and the well established neurotoxicity of TOCP suggest that due care be exercised to avoid exposure to TOCP.

49.4 SAMPLING AND ANALYSIS CONSIDERATIONS

Determination of the concentration of TOCP in soil and water requires collection of a representative field sample and laboratory analysis. Care is required to prevent losses during sample collection and storage. Soil and water samples should be collected in glass containers; extraction of samples should be completed within 7

days of sampling and analysis completed within 30-40 days. In addition to the targeted samples, quality control samples such as field blanks, duplicates, and spiked matrices should be included in the analytical program.

TOCP is not included among the EPA-designated priority pollutants, and an EPA-approved procedure for the analysis of TOCP is not available. However, EPA Method 8140 is a recommended procedure for the analysis of organophosphorus pesticides in ground-water and waste samples (63) and should be an appropriate method for the analysis of TOCP. In this method, aqueous samples are extracted at neutral pH with methylene chloride using a separatory funnel or a continuous liquid-liquid extractor. Solid samples are extracted using either soxhlet extraction or sonication methods; neat and dilute organic liquids that contain a high concentration of these compounds may be analyzed by direct injection. An aliquot of the sample or concentrated sample extract is injected onto a gas chromatographic (GC) column for separation of the semi-volatile organics. Detection of the individual organophosphorus pesticides is then accomplished by either a thermionic detector or a flame photometric detector (FPD). The FPD is more selective for phosphorus than the N/P.

In addition, a NIOSH-approved method for the analysis of levels of TOCP in air samples is available (40). Sampling and analysis is performed by collection of TOCP on a filter, followed by extraction with ether, and gas chromatographic analysis using a flame photometric detector.

A detection limit for TOCP using these methods was not determined but would be in the range of 1-10 $\mu g/L$ for aqueous samples, 1-10 $\mu g/g$ for nonaqueous samples which have been extracted and part-per-million (ppm) range for samples which have been directly injected.

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Note: The nonsequential numbers of the references reflect the order of references as they appear in the master bibliography.

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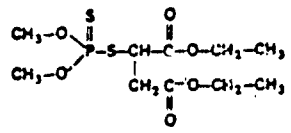
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COMMON SYNONYMS:	CAS REG.NO.: 121-75-5 FORMULA: $C_{10}H_{19}O_6PS_2$ NIOSH NO: WM8400000 STRUCTURE: 	AIR W/V CONVERSION FACTOR at 25°C (1098) 13.7 mg/m³ ≈ 1 ppm; 0.073 ppm ≈ 1 mg/m³ MOLECULAR WEIGHT: 330.36
Butanedioic acid, [(dimethoxyphosphinothioyl)-thio]-diethyl ester Carbophos Malathion		

REACTIVITY	For compatibility classification purposes, malathion is considered to be in the reactivity group of organophosphates, phosphothioates and phosphodithioates. Such substances typically generate heat in reactions with alkali or alkaline earth elemental metals, heat and toxic gases in reactions with mineral acids, and heat and possible explosion with caustics. Hazardous reactions with azo or diazo compounds, hydrazines or organic peroxides or hydroperoxides are also possible. More specific sources indicate that malathion may be incompatible with strong oxidizers, that it is hydrolyzed at various rates above a pH of 7, and that prolonged contact with iron or iron-bearing material may cause breakdown of the material. Reaction with a strong base may generate excessive heat, storage at 50-115°C leads to a non-hazardous decomposition reaction (that produces several toxic products), and heating above 150°C causes rapid decomposition (54, 59, 507, 511).

PHYSICO-CHEMICAL DATA	• Physical State: Liquid (at 20°C)	(69)
	• Color: Deep brown to yellow	(69)
	• Odor: Skunk-like	(60)
	• Odor Threshold: No data	
	• Density: 1.2315 g/mL (at 25°C)	(23)
	• Freeze/Melt Point: 2.90°C	(69)
	• Boiling Point: 156.00 to 157.00°C at 0.7 mm Hg	(69)
	• Flash Point: >162.8°C	(60,507)
	• Flammable Limits: No data	
	• Autoignition Temp.: No data	

PHYSICO-CHEMICAL DATA (Cont.)	• Vapor Pressure: 6.60E-05 mm Hg (at 20°C)	(1219)
	• Satd. Conc. in Air: 1.2000E-01 mg/m³ (at 20°C)	(1219)
	• Solubility in Water: 1.45E+02 mg/L (at 20°C)	(38)
	• Viscosity: No data	
	• SurfaceTension: 3.7100E+01 dyne/cm (at 24°C)	(60)
	• Log (Octanol-Water Partition Coeff.): 2.84	(1488)
	• Soil Adsorp. Coeff.: 1.80E+03	(1211)
	• Henry's Law Const.: 2.00E-08 atm·m³/mol (at 20°C)	(1216)
	• Bioconc. Factor: 3.30E+01 (estim)	(37)

PERSISTENCE IN THE SOIL-WATER SYSTEM	Fairly immobile and non-persistent in soil water systems due to moderate sorption and relatively rapid degradation by hydrolysis (at pH >7) and biodegradation. Photolytic degradation is important for surface waters and soil.

PATHWAYS OF EXPOSURE	The primary pathway of concern from soil/ground-water systems is the migration of malathion to ground water drinking water supplies. However, the potential for adsorption and degradation make the contamination of water supplies with malathion less likely than with other chemicals. Exposures through inhalation or bioaccumulation are not generally expected to be significant.

HEALTH HAZARD DATA	Signs and Symptoms of Short-term Human Exposure: (38) After ingestion of malathion, loss of appetite, nausea, vomiting, abdominal cramps and diarrhea may appear within 2 hours. Inhalation results in chest tightness, blurred vision, constricted pupils, headache and watering of the mouth. After skin absorption, sweating and twitching in the area of absorption may occur. Acute Toxicity Studies: INHALATION: LC_{50} 15 mg/m³ Mouse (1374) value is >15 ORAL: LD_{50} 370 mg/kg Rat (47) SKIN: LD_{50} 4444 mg/kg Rat (47) Long-Term Effects: Decreased cholinesterase levels Pregnancy/Neonate Data: Negative Genotoxicity Data: Limited evidence Carcinogenicity Classification: IARC - Group 3 (Not classifiable as to its carcinogenicity to humans) NTP - No evidence EPA - No data
HANDLING PRECAUTIONS (38)	Handle chemical only with adequate ventilation • Vapor concentrations of 15 mg/m³-150 mg/m³: any supplied-air respirator or self-contained breathing apparatus; any chemical cartridge respirator with organic vapor cartridge and dust fume and mist filters, including pesticide respirators which meet the requirements of this class • 150-750 mg/m³: any supplied air respirator or self-contained breathing apparatus with full facepiece • Chemical goggles if there is probability of eye contact • Full-body coveralls and impervious gloves.

ENVIRONMENTAL AND OCCUPATIONAL STANDARDS AND CRITERIA

AIR EXPOSURE LIMITS:

Standards
- OSHA TWA (8-hr): 10 mg/m³ (total dust); 5 mg/m³ (respirable) (skin)
- AFCSH PEL (8-hr TWA): 10 mg/m³ (total dust); 5 mg/m³ (respirable) (skin): STEL (15-min): 30 and 15 mg/m³, respectively

Criteria
- NIOSH IDLH (30-min): 5000 mg/m³
- NIOSH REL (10-hr TWA): 15 mg/m³
- ACGIH TLV® (8-hr TWA): 10 mg/m³ (skin)
- ACGIH STEL (15-min): None established

WATER EXPOSURE LIMITS:

Drinking Water Standards
None established

EPA Health Advisories and Cancer Risk Levels
None established

WHO Drinking Water Guideline
No information available.

EPA Ambient Water Quality Criteria
- Human Health (355)
  - No criterion established; malathion is not a priority pollutant.
- Aquatic Life (355)
  - No criterion established; malathion is not a priority pollutant.

REFERENCE DOSES: (3744)
0.02 mg/kg/day

REGULATORY STATUS (as of 01-MAR-89)

Promulgated Regulations

- Federal Programs

Clean Water Act (CWA)
Malathion is designated a hazardous substance. It has a reportable quantity (RQ) limit of 45.4 kg (347, 3764).

Comprehensive Environmental Response Compensation and Liability Act (CERCLA)
Malathion is designated a hazardous substance under CERCLA. It has a reportable quantity (RQ) limit of 45.4 kg (3766).

Federal Insecticide, Fungicide and Rodenticide Act (FIFRA)
The combination of malathion in methyl eugenol is exempt from the requirement of a tolerance on all raw agricultural commodities when used in Oriental fruit fly eradication programs in accordance with the following specifications:

- One part technical malathion to three parts methyl eugenol;
- The combination must be impregnated on a carrier or mixed with a gel approved under 40CFR180.1001(d);
- The maximum actual dosage per application per acre shall be 28.35 g methyl eugenol and 9.45 g technical malathion (984).

Tolerances have been established for malathion residues in or on raw agricultural commodities. Levels range from 0.1 to 135 ppm (976). Pesticide registration standards for malathion have been issued by EPA (3798).

Marine Protection Research and Sanctuaries Act (MPRSA)
Ocean dumping of organohalogen compounds as well as the dumping of known or suspected carcinogens, mutagens or teratogens is prohibited except when they are present as trace contaminants. Permit applicants are exempt from these regulations if they can demonstrate that such chemical constituents are non-toxic and non-bioaccumulative in the marine environment or are rapidly rendered harmless by physical, chemical or biological processes in the sea (309).

Occupational Safety and Health Act (OSHA)
Employee exposure to malathion shall not exceed an 8-hour time-weighted average (TWA) of 10 mg/m^3 for total dust or 5 mg/m^3 for respirable fraction. Employee skin exposure shall be prevented/reduced through the use of protective clothing and practices (3539).

Hazardous Materials Transportation Act (HMTA)
The Department of Transportation has designated malathion as a hazardous material with a reportable quantity of 45.4 kg, subject to requirements for packaging, labeling and transportation (3180).

Food, Drug and Cosmetic Act (FDCA)
Malathion may be safely used in paper trays intended for use only in the drying of grapes. It may not exceed 100 mg per square foot. Total residues of malathion resulting from the drying of grapes on treated trays and from application to grapes before harvest shall not exceed 12 ppm on processed ready-to-eat raisins. Residues of malathion in refined safflower oil from application to the growing safflower plant shall not exceed 0.6 ppm (886).

- State Water Programs

ALL STATES
All states have adopted EPA Ambient Water Quality Criteria and NPDWRs (see Water Exposure Limits section) as their promulgated state regulations, either by narrative reference or by relisting the specific numeric criteria. These states have promulgated additional or more stringent criteria:

CALIFORNIA
California has an action level of 160 µg/L (ppb) for malathion in drinking water (3098).

FLORIDA
Florida has a water quality criterion of 0.1 µg/L for malathion in the public water supply (Class I, II and III surface waters) (3220).

KANSAS
Kansas has an action level of 140 µg/L for malathion in ground-water (3213).

NEW YORK
New York has a water quality standard of 7 µg/L for ground-water classed for drinking water supply, and an MCL of 50 µg/L for drinking water (3501).

Proposed Regulations

- Federal Programs

No proposed regulations are pending.

- State Water Programs

No proposed regulations are pending.

MOST STATES
Most states are in the process of revising their water programs and proposing changes in their regulations which will follow EPA's changes when they become final. Contact with the state officer is advised. Changes are projected for 1989-90 (3683).

EEC Directives

Directive on Drinking Water (533)
The mandatory values for total pesticides in surface water treatment categories A1, A2 and A3 used or intended for abstraction of drinking water are 0.001, 0.0025 and 0.005 mg/L, respectively. There are no guideline values.

Directive Relating to the Quality of Water for Human Consumption (540)
The maximum admissible concentration for malathion is 0.1 µg/L. The total maximum allowable concentration for pesticides and related products is 0.5 µg/L.

Directive on Ground-Water (538)
Direct discharge into ground-water (i.e., without percolation through the ground or subsoil) of organophosphorous compounds, organohalogen compounds and substances which may form such compounds in the aquatic environment, substances which possess carcinogenic, mutagenic or teratogenic properties in or via the aquatic environment and mineral oils and hydrocarbons is prohibited. Appropriate measures deemed necessary to prevent indirect discharge into ground-water (i.e., via percolation through ground or subsoil) of these substances shall be taken by member countries.

Directive on Bathing Water Quality (534)
When inspection of a bathing area shows that heavy metals, pesticides or cyanides may be present, concentrations should be checked by competent authorities.

Directive on the Discharge of Dangerous Substances (535)
Organohalogens, organophosphates, petroleum hydrocarbons, carcinogens or substances which have a deleterious effect on the taste and/or odor of human food derived from aquatic environments cannot be discharged into inland surface waters, territorial waters or internal coastal waters without prior authorization from member countries which issue emission standards. A system of zero- emission applies to discharge of these substances into ground-water.

Directive on Marketing and Use of Dangerous Substances (541)
Malathion may not be used in ornamental objects intended to produce light or color effects by means of different phases.

Directive on Classification, Packaging and Labeling of Pesticides (786)

Malathion containing more than 1.8% isomalathion is listed as a Class II/c substance and malathion containing less than 1.8% isomalathion is listed as a Class II/d substance. Both are subject to packaging and labeling regulations.

Directive on the Classification, Packaging and Labeling of Dangerous Substances (787)
Malathion is classified as a harmful substance and is subject to packaging and labeling regu ations.

EEC Directives - Proposed
Proposal for a Council Directive on the Dumping of Waste at Sea (1793)
EEC has proposed that the dumping of pesticides at sea be forbidden without prior issue of a special permit

Resolution on a Revised List of Second-Category Pollutants (545)
Malathion is one of the second-category pollutants to be studied by the Commission in the programme of action of the European Communities on Environment in order to reduce pollution and nuisances in the air and water. Risk to human health and the environment, limits of pollutant levels in the environment, and determination of quality standards to be applied will be assessed.

50.1 MAJOR USES

Malathion, introduced in 1950, has a wide range of agricultural and horticultural uses, but is employed primarily as an insecticide and acaricide on fruits, vegetables and ornamental plants. It is also used to control animal ectoparasites, flies, lice and mosquitoes (1118, 1300). It is available in a variety of formulations, either alone, or combined with other insecticides or fungicides. Early samples were marketed as a technical-grade with a purity of 65-77%; with improved synthesis methods, the purity of malathion now exceeds 99% (17, 1037).

50.2 ENVIRONMENTAL FATE AND EXPOSURE PATHWAYS

50.2.1 Transport in Soil/Ground-water Systems

50.2.1.1 Overview

Malathion is expected to be relatively immobile in the soil/ground-water environment when present at low concentrations (dissolved in water). Bulk quantities of the liquid chemical (e.g., from a spill, heavy spray application or improper disposal of excess formulations) could be transported down through the unsaturated zone. However, most studies have shown that normal application of malathion sprays to soil surfaces do not result in transport of the chemical to any significant distance below the soil surface. Furthermore, malathion is readily susceptible to a number of degradation pathways (hydrolysis, photolysis, biodegradation) so that residuals from normal applications have fairly short half-lives (days to weeks) in the topsoil environment. The environmental persistence is strongly dependent upon temperature, soil pH, organic carbon content and microbiological activity, as well as other parameters. Under special conditions (e.g., no sunlight, low temperature, low soil pH, high soil organic carbon content), the half-life of malathion in the environment could be quite long (months to years). Such conditions, in combination with high infiltration rates, could allow ground water to be contaminated.

Environmental transport pathways for malathion can be generally assessed by using an equilibrium partitioning model as shown in Table 50-1. These calculations predict the partitioning of low soil concentrations of malathion among soil particles, soil water and soil air. The estimates for the unsaturated topsoil model show that while essentially all of the chemical (99.7%) is sorbed to the soil, a small amount (0.3%) is in solution and could be transported down with percolating waters. Negligible amounts of the chemical are predicted to be in the soil air and thus volatilization losses would be expected to be very small. In saturated, deep soils (containing no air and negligible soil organic carbon), the model predicts substantially more malathion (11.7%) to be in the mobile ground-water phase.

TABLE 50-1
EQUILIBRIUM PARTITIONING CALCULATIONS FOR MALATHION IN MODEL ENVIRONMENTS[a]

Soil Environment	Estimated Percent of Total Mass of Chemical in Each Compartment		
	Soil	Soil-Water	Soil-Air
Unsaturated topsoil at 25°C[b,c]	99.7	0.29	7.2E-07
Saturated deep soil[d]	88.3	11.7	-

a) Calculations based on Mackay's equilibrium partitioning model (34, 35, 36); see Introduction in Volume 1 for description of model and environmental conditions chosen to represent an unsaturated topsoil and saturated deep soil. Calculated percentages should be considered as rough estimates and used only for general guidance.
b) Utilized estimated soil sorption coefficient: K_{oc} = 1800 (1211).
c) Henry's law constant taken as 2.0E-08 atm · m³/mol at 25°C (1216).
d) Used sorption coefficient $K_p = 0.001 \times K_{oc}$.

Many of the early studies on transport and fate of malathion in the soil/ground-water system are described in references 1374, 1203-1208 and 1216.

50.2.1.2 Sorption on Soils

There appear to be relatively few studies focusing on the soil sorption properties of malathion. In part, this is because studies have shown malathion to be readily degraded and thus not problematic with regard to its soil leaching potential.

Values of the equilibrium soil sorption constant, K_{oc}, for malathion have been reported as 2300 (1209), 930 (1210) and 1797 (1211); the value, 1797, is an average of measurements for 20 soils and has a coefficient of variation of 66%. These values indicate that sorption of malathion on topsoils (containing >0.1% organic carbon) is of moderate strength, i.e., most of the chemical will be sorbed to the soil, but not so strongly that leaching is prevented. As with all neutral organic chemicals, the extent of soil sorption is directly proportional to the soil organic carbon content. For low organic carbon soils (e.g., clays), the extent of sorption may also depend on other properties of the soil such as surface area, cation exchange capacity and degree of hydration (1374). Under certain conditions, malathion can be sorbed into the interlayer spaces of montmorillonite clays (1374, 1212).

Malathion sorption to four soils has been shown to decrease slightly with increasing temperature over the range of 15°C to 40°C (1213). For example, the Freundlich sorption constant, K, for malathion decreased 18% (average of 4 soils) when the temperature was raised from 15°C to 30°C (1213). By contrast, malathion sorption to natural and synthetic humic acids has been shown to increase slightly with increasing temperature, possibly due to an increase in the number of sorption sites on the humic acids at the higher temperatures (1214).

Other laboratory, field and modeling studies on the downward movement of soil-applied malathion tend to support the conclusion that sorption is strong enough (in conjunction with easy degradation) to prevent contamination of ground water aquifers (1374, 1215, 1216). However, Bomberger et al. (1209) conclude from modeling studies - which modeled transport but not degradation - that "malathion is not strongly adsorbed and could leach deeply into the soil." In one calculation, assuming application of 305 cm rain water to a typical soil with a field capacity of 30%, they estimated the depth of maximum concentration of malathion to be 102 cm.

50.2.1.3 Volatilization from Soils

Malathion has a low vapor pressure (6.6E-08 mm Hg at 20°C (1219)) and a low Henry's law constant (2.0E-08 atm · m^3/mol at 20°C (1216)). These values, coupled with malathion's moderate extent of soil and sediment sorption, imply that volatilization from soils (or surface waters) should not be an important transport pathway. The relative insignificance of volatilization has been demonstrated in a variety of laboratory or field tests (1216, 1217, 1218) and modeling studies (1209). Volatilization losses in these studies were typically less than one percent of the malathion present. Volatilization losses from the surfaces of foliage or structures (e.g., after spray applications) could be substantially larger.

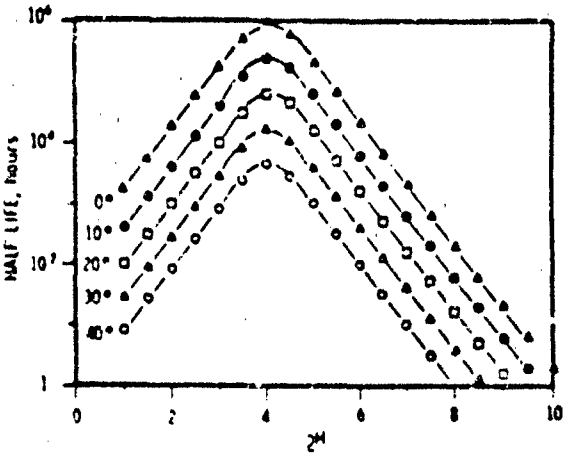
50.2.2 Transformation Processes in Soil/Ground-water Systems

Malathion is susceptible to a number of degradation processes - including hydrolysis, biodegradation and photolysis - and is not considered to be persistent in the environment.

Evidence for the photolytic degradation of malathion (in surface waters or surfaces exposed to the light) has been reported (1204, 1205, 1220, 1222). Wolfe et al. (1205) concluded that the photolysis of malathion by sunlight is too slow to compete with chemical degradation in pure water. However, some naturally occurring substances in surface waters appear to catalyze the photolysis, and photolytic half-lives as low as 16 hours (in Suwannee River water) have been estimated (1204, 1222). The photolytic half-life for malathion on glass plates exposed to artificial sunlight has been measured as 51 hours (1220).

Data on the importance of hydrolysis in the environmental degradation of malathion are provided in references 1374, 1203-1205, 1207, 1216-1218, 1221 and 1222. The 1976 review by Wolfe et al. (1205) concluded that hydrolysis of malathion was likely to be the major pathway for its transformation in basic natural waters (pH greater than 7). The hydrolysis products are a mixture of malathion acids, fumaric acid and its ethyl esters, and O,O-diethylphosphorodithioic acid (1205). The rate of hydrolysis, and subsequent environmental half-life, is strongly dependent on both pH and temperature as shown in Figure 50-1. The hydrolysis half-life at 20°C and pH 7, for example (from Figure 50-1), is seen to be about 200 hours (8.3 days). Chapman and Cole (1207) summarize hydrolysis half-life measurements from several investigations, including their own, as shown in Table 50-2.

Chapman and Cole (1207) conducted further experiments to see if the pH dependence of the hydrolysis of malathion observed in aqueous solution could also be observed in heterogeneous, mostly solid systems with low microbial activity. Using malathion concentrations of 1 and 20 ppm on three types of alumina (acid, neutral, basic) containing 15% water, they found that the chemical was poorly recovered and/or rapidly degraded on these solids irrespective of pH. Subsequent tests were conducted with natural soils at different pH values. Malathion was again rapidly degraded although the results showed some anomalous pH dependence which suggested that other processes in addition to chemical degradation were involved.



Source: Wolfe et al. (1221)

FIGURE 50-1
TEMPERATURE AND pH EFFECTS ON MALATHION DEGRADATION

TABLE 50-2
HYDROLYSIS HALF-LIVES FOR MALATHION IN AQUEOUS SOLUTIONS AT TEMPERATURES NEAR 20°C

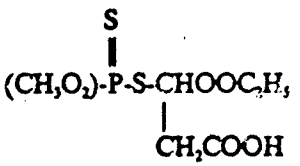
pH	No. of Data Points	Hydrolysis Half-Life (weeks) Mean	Range
6	6	7.8	1 - 21
7	5	3.0	1 - 7
8	5	0.8	0.5 - 1.0

Source: Chapman and Cole (1207).

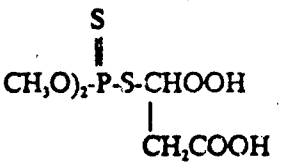
Chapman and Harris (1221) have shown that the hydrolysis of malathion is catalyzed by the cupric, Cu(II), ion over a range of pH values. They cite other studies indicating that the hydrolysis of organophosphorus compounds can be catalyzed by other types of chemicals including nitrogenous organic bases, metal ions (type unspecified) and metal chelates.

Studies on the biodegradation of malathion are reviewed in a number of reports (1374, 1203, 1206, 1211, 1216). The general conclusion is that under normal conditions, malathion is readily biodegradable and that biodegradation probably competes with hydrolysis as the most important environmental degradation pathway. Rao and Davidson (1211), using a variety of reported data from laboratory tests simulating aerobic conditions, estimate a mean biodegradation half life of 0.8 days (87% coefficient of variation).

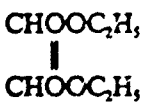
Malathion has been shown to be degradable by a variety of bacteria and fungi, and can be the sole source of carbon and/or phosphorus for some species (1374, 1223, 1224, 1225). The major metabolite produced from bacterial action is beta-malathion monoacid (I). Small amounts of malathion dicarboxylic acid (II), diethyl maleate (III), and O,O-dimethyl phosphorodithioic acid (IV) are also produced.



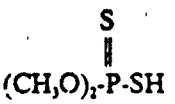
I



II



III



IV

Paris et al. (1226), using microorganisms from 14 natural surface waters, showed that malathion biodegradation can be described with a second order rate equation:

$$-\frac{d[S]}{dt} = k\,[B]\,[S]$$

where k is a second-order rate constant (with units of liters per organism per hour), [B] is the concentration of bacteria (organisms/liter), [S] is the concentration of malathion (mg/L), and t is time (hr). The mean value of k for malathion was (4.4 ± /2.9E-11 liters per organism per hour; this is for the 14 surface waters whose average temperature was 21°C.

50.2.3 Primary Routes of Exposure from Soil/Ground-water Systems

The above discussion of fate pathways suggests that malathion is effectively nonvolatile, is moderately to strongly sorbed to soil, and has a low potential for bioaccumulation. These fate characteristics suggest several potential exposure pathways.

Volatilization of malathion from a disposal site is not likely to represent an important exposure pathway. There is some potential for drinking water contamination through the movement of this compound with ground water, particularly in sandy soils. This compound was not reported in Mitre's compilation (83) of compounds

detected at the 546 National Priority List (NPL) sites. This may be partially due to the adsorption of malathion to soil, but is probably also due to its susceptibility to degradation.

Discharges of malathion to surface waters from soil/ground-water systems would probably not represent a significant source of exposure due to malathion's low potential for bioaccumulation and its degradability.

50.2.4 Other Sources of Human Exposures

Malathion has been registered for use as an insecticide for over 20 years. As a result of its wide use, there are a number of sources of exposure to malathion.

Malathion was detected in 50% of 123 air samples at 10 U.S. locations. The maximum concentration was 220 ng/m^3 and the mean concentration was 7.5 ng/m^3 (1242). These data suggest that inhalation may represent a source of exposure.

NRC (213) reported that malathion had not been detected in drinking water at that time. In addition, Carey and Kutz (1242) reported finding malathion in 0.3% of the samples in the National Surface Water Monitoring Program from 1976-1980 with a maximum value of 0.18 mg/L. Malathion was not detected in the sediment in this monitoring program.

Malathion is commonly found in foods. It is included in the U.S. Food and Drug Total Diet Study to determine dietary intake. Over the years 1976-1978, the average dietary intake for adults ranged from 0.128-0.154 μg/kg body weight/day. In 1979, the average daily intake was 0.265 μg/kg/day. Average daily intakes for infants and toddlers over the same time period ranged from 0.064-0.259 μg/kg/day (1244, 1245). In Canada, the average daily intake over the years 1976-1978 was 0.012 μg/kg/day (1246). The largest source of exposure appeared to be grain and cereal products, and oils and fats.

50.3 HUMAN HEALTH CONSIDERATIONS

Malathion is available in a variety of different formulations, including a number of formulations that contain malathion in combination with other insecticides and/or fungicides. The toxicity of commercial malathion formulations, therefore, is greatly dependent on ingredients; the content of impurities, particularly isomalathion which potentiates the toxicity of malathion; and the presence of toxic degradation products such as malaoxon that may form during storage (1098, 1374). Early samples of malathion were marketed as technical-grade, with a purity of 65-77%; the purity of currently produced malathion exceeds 99% (17, 1037).

50.3.1 Animal Studies

50.3.1.1 Carcinogenicity

No evidence of carcinogenicity was found in mice and rats administered malathion (purity 95%) in the diet in either of two studies carried out by the NCI. The initial study, done in 1978, was conducted in Osborne-Mendel rats and $B6C3F_1$ mice. Mice were given doses of 8000 or 16,000 ppm and rats received 4700 or 8150 ppm over an 80 week period. The animals were observed for an additional period of 14 to 33 weeks. A significant increase in hepatocellular carcinoma in male mice was noted, but it was comparable to the historical incidence in the laboratory and not considered to be associated with malathion administration. There was no evidence of carcinogenicity in male or female Osborne-Mendel rats (1354).

In the second study, F344 rats were fed diets containing 2000 or 4000 ppm for 103 weeks and observed for an additional 2-3 weeks. No tumors were found in either sex that could be related to malathion administration; the females may not have received the maximum tolerated dose (1355). A recent NTP re-evaluation of the histopathology of these malathion studies found no substantive reason to warrant altering the original conclusion that malathion was not carcinogenic (1356). Reuber (1357) has published a dissenting view; he believes malathion to be carcinogenic in both rat species.

50.3.1.2 Genotoxicity

There is conflicting evidence for the mutagenicity of malathion. Negative results have been obtained in almost all strains of Salmonella typhimurium in the reverse mutation assay either in the presence or absence of rat or hamster liver microsomal activation (1358, 1361, 1363, 3276); however, a positive result with metabolic activation was reported in strain TA100 (1360), but this result was not found in other laboratories using this strain. Imamura and Talcott (3323) tested purified malathion as well as three impurities often found in malathion in Salmonella strains TA97, TA98 and TA100 with and without metabolic activation in a preincubation assay as well as the plate incorporation assay and found no evidence for genotoxicity. They concluded that Salmonella is not a good indicator organism for testing organophosphates. Weak mutagenic activity was detected in a reverse mutation assay using B. subtilis TKJ6321 (1361).

Negative effects were observed in a sex-linked recessive lethal mutation test in Drosophila melanogaster fed solutions containing 0.25 or 0.5 mg/L malathion (1362). Velazquez et al. (3812) also observed negative results when they fed Drosophila males as adults or larvae and looked for sex chromosome loss and nondisjunction as well as sex-linked recessive lethals.

Al-Sabti (3014) exposed rainbow trout to a concentration of 0.01 or 0.02 microliters for 72 hrs and observed significant increases in chromosome aberrations in gill and kidney cells.

Nicholas et al. (1364) treated human fetal lung fibroblasts with malathion (99%) and observed a significant increase in sister chromatid exchanges after a single exposure to 40 mg/mL or two exposures to 20 mg/mL. Similar results were obtained in Chinese hamster ovary cells exposed to 0.3 to 1 mM of 99% malathion by Nishio and Uyeki (1365) and in Chinese hamster V79 cells exposed to 40 μg/mL of 94% malathion by Chen et al. (1366). Galloway et al. (3235) reported positive results for sister chromatid exchanges with or without metabolic activation in Chinese hamster ovary cells, but these cells showed no increase in chromosome aberrations without metabolic activation; positive results for chromosome aberrations were found only with activation.

In in vivo studies, Degraeve et al. (1367) observed no dominant lethals and no chromosome damage in bone marrow cells, spermatogonia, and primary spermatocytes of Q strain mice receiving 8 ppm malathion in drinking water 5 days per week for 7 weeks. Degraeve and Moutschen (3165) observed similar results when male mice were injected intraperitoneally with 300 mg/kg malathion. No dominant lethality was observed in mice fed 1200, 2500 or 5000 mg/kg diet for 7 weeks (1363). Dzwonkowska and Hubner (3191) called malathion weakly clastogenic ($p < 0.05$) in the bone marrow cells of female Syrian golden hamsters injected intraperitoneally with doses up to the LD_{50} (2400 mg/kg) and sacrificed 24 hours after injection. Positive micronucleus test results were reported by Dulout et al. (3185) when they treated male mice with malathion cutaneously or via intraperitoneal injection. Surprisingly, higher frequencies of micronuclei were observed in the bone marrow cells of mice treated cutaneously than in the mice treated intraperitoneally.

Trinh van Bao et al. (3725) found significantly ($p < 0.001$) high frequencies of chromosomal aberrations and breaks in lymphocytes of 14 patients who had been occupationally exposed to malathion (cutaneously or via inhalation) or who had attempted suicide by drinking malathion. One month later 12 of these patients still had high frequencies, but 6 months after exposure, the number of aberrations was approaching those of the unexposed controls.

50.3.1.3 Teratogenicity, Embryotoxicity and Reproductive Effects

No evidence of teratogenicity or embryotoxicity has been found in rats given maternally tolerated doses of malathion during pregnancy (1359). The effect of a single intraperitoneal dose on rat fetuses was evaluated by Kimbrough and Gaines (1159) who injected dams with 600 or 900 mg/kg on the 11th day of pregnancy. The fetuses were removed after the 20th day. No adverse effects were seen.

No teratogenic effects were noted in the offspring of male and female rats fed dietary concentrations of 4000 mg/kg (approximately 240 mg/kg bw/day) for 2

generations. However, the survival of the progeny on days 7 and 21 after birth was found to be reduced with the survivors showing growth retardation (1369). Lechner and Abdel-Rohman (3392) treated female rats with 1 or 50 mg/kg/day of malathion by gavage for 3 months prior to and throughout gestation. No increases were seen in skeletal or visceral anomalies in the offsprings of either treatment group; however, an increase in external hemorrhagic spots was observed in the 50 mg/kg/day pups. No teratogenic or embryotoxic effects were observed in Wistar rats given doses of 50 to 300 mg/kg by gavage on days 6 through 15 of gestation (1370).

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During the 11th and 12th week of pregnancy a woman repeatedly washed her hair with a 0.5% malathion lotion. Although no maternal toxicity was noted, an infant girl exhibiting an amyoplasia congenita-like condition was delivered by cesarean section at 38 weeks. There was no evidence of genetic etiology. Various aspects of causal association were discussed (3398).

50.3.1.4 Other Toxicologic Effects

50.3.1.4.1 Short-term Toxicity

The acute toxicity and LD_{50} values of malathion depend upon the purity of the compound tested (1359). The oral LD_{50} values of 65% malathion in male mice and male rats were 1260 and 369 mg/kg, respectively, and those of 99% malathion were 4059 and 5843 mg/kg, respectively (1359). The oral LD_{50} value of 99.7% pure malathion in male rats was approximately 10,000 mg/kg, while malaoxon, the active metabolite, has an oral LD_{50} value of 23-158 mg/kg for the rat (1098). Sex differences in susceptibility to the effects of malathion are generally confined to rodents given malathion orally, with males found to be less sensitive to malathion than females. This difference has been attributed to differences in the rates of detoxification (1300).

The toxic effects of malathion in both animals and humans is due to inhibition of acetylcholinesterase, leading to an accumulation of endogenous acetylcholine (1359). Signs of malathion poisoning in both animals and man include headache, dizziness, weakness, tremor, nausea, abdominal cramps, diarrhea, and sweating. Blurred vision, chest tightness, wheezing cough, pulmonary edema, tearing, salivation, slow heart beat and toxic psychosis are common. In severe cases convulsions and unconsciousness may occur (1373).

In dogs, an intravenous dose of 100 mg/kg had no apparent effect, while 200 mg/kg produced signs of cholinesterase inhibition and 250 mg/kg was lethal (1371). A single oral dose of 300 mg/kg caused approximately the same inhibition of acetylcholinesterase as about 15-20 mg/kg inhaled by rabbits exposed to an aerosol containing 123 mg/m^3 for 6 hours (1372). Rats, mice and guinea pigs exposed to vapor concentrations up to 67 mg/m^3, 8 hours per day, 5 days per week for 4 weeks experienced no significant cholinesterase depression or any other toxic effects (1371).

Animal experiments indicate that dermal application of malathion can cause cholinergic effects and death. Single applications of 2460 to 6150 mg/kg (90% purity) produced some toxicity in rabbits (12). Dermal LD_{50} values in rats have been reported to be greater than 4400 mg/kg (1363).

Undiluted malathion dropped on a rabbit's eye caused slight immediate irritation with conjunctival hyperemia and edema of the lids, but the eye returned to normal within 24 hours (19).

50.3.1.4.2 Chronic Toxicity

Long-term oral toxicity studies of malathion have been conducted in rats for periods of up to 2 years. No signs of intoxication were observed in rats fed diets containing 4000 ppm for 5 months or 1000 ppm for 6 months (1369, 1375). Exposure of rats to diets containing 500-20,000 ppm for two years caused significant depression of cholinesterase activity in red cells at all exposure levels with food intake and growth decreased at the 20,000 ppm level (1376). Hepatocyte degeneration as well as prolongation of the prothrombin time and partial thromboplastin time were seen in female Sprague-Dawley rats that received 1 ppm malathion in drinking water for 6 months (1113).

Intraperitoneal injection of malathion in rats for 60 days resulted in a no adverse effect level of 100 mg/kg while dosages of 200 and 300 mg/kg resulted in mortality rates of 60 and 100%, respectively (1377).

50.3.2 Human and Epidemiologic Studies

50.3.2.1 Short-term Toxicologic Effects

Malathion has a relatively low order of toxicity in comparison with other organophosphates (46). The apparent reason for this is the rapid detoxification of both malathion and malaoxon, a metabolite of malathion, by esterases in the liver and other organs. Malathion has only a slight inhibitory action on cholinesterase but malaoxon is an active inhibitor and therefore more toxic (46). Early reports of malathion toxicity described more severe toxic effects due to the presence of malaoxon and other impurities. The purity of the malathion currently used (99%) has resulted in a corresponding decrease in observed acute toxicity (17). The human oral lethal dose is estimated to range from 0.4-1 g/kg (1300).

Manifestations of acute poisoning in humans are similar to those in animals. The first symptoms to appear after inhalation are respiratory and ocular. These include tightness in the chest, wheezing, pinpoint pupils and blurred vision. Gastrointestinal effects, such as nausea, vomiting and diarrhea appear 15 minutes to 2 hours after ingestion while symptoms such as localized sweating will appear 15 minutes to 4 hours after percutaneous exposure (1378). There is a single anecdotal report of an association between a brief inhalation exposure to malathion and subsequent development of aplastic anemia (1379).

Almost all reports of fatalities from malathion have resulted from ingestion. The principal cause of death is respiratory failure (1380). Harris et al. (1381) described the case of a 45-year-old woman who ingested an unknown amount of malathion. Six hours later she was admitted to a hospital, unconscious, and in total cardiac and respiratory arrest. Seizures developed about 8 hours after admission. Hyperglycemia and moderate bradycardia were also noted. Two days after admission, the woman showed slight voluntary movement and responded to external stimuli. However, ventricular fibrillation occurred 4 hours later. Cholinesterase activity was absent from both red cells and plasma. The woman died 5.5 days after ingestion. Autopsy revealed generalized edema, severe pulmonary edema and bronchopneumonia which were probably indirect effects of shock and respiratory failure. Ingestion of 0.5 mg/kg has resulted in cyanosis, incontinence, miosis, hypotension and respiratory distress (1382, 1383), however, ingestion of 8 ounces has been survived (1393).

Intramuscular injection of 3 mL resulted in hypotonia of the limbs, excessive sweating, and convulsions with the individual recovering in 2 weeks (1385).

As a suicide attempt, an adult male injected 3 mL (1.8 g) of 50% malathion intravenously (3413). Two hours after the injection the man complained of headache, nausea, and increased urination. Blood pressure was 100/60, pulse was 60, respirations were 20 and body temperature was 98 degrees F. The patient was also experiencing hallucinations and delusions. Serum pseudocholinesterase (PChE) levels were undetectable for 24 hours following the injection but increased to 9 IU/ml (normal 7-19) at 7 days. As PChE levels increased, serum levels of malathion decreased. The patient was released to a psychiatric hospital after 2 days of hospitalization.

In a group of workers with an average exposure of 3.3 mg/m^3 for 5 hours (maximum of 56 mg/m^3), the cholinesterase levels in the blood were not significantly lowered and none exhibited signs of cholinesterase inhibition (46).

A 10% malathion solution applied to the skin as a dressing and retained in contact with the skin for 2 days produced sensitization. Solutions of 0.1 and 1.0% had no effect (1386). Application of 1.1% malathion dust for 8 hours daily for 3 weeks produced no significant depression of red cell cholinesterase (1387).

50.3.2.2 Chronic Toxicologic Effects

Long-term studies of malathion have been conducted in human volunteers by both the oral and inhalation routes. Golz (1388) exposed 12 men to a total of 84 one-hour exposures to malathion aerosol for 42 consecutive days. Initial concentrations were calculated to be 5.3, 21.2 or 84.8 mg/m^3 No cholinergic signs or symptoms were observed, however, there was moderate irritation of the nose and conjunctiva.

Moeller and Rider (1389) fed 10 men daily doses of malathion dissolved in corn oil to determine the amount that could be ingested over an extended time period without causing depression of cholinesterase activity. Five subjects each received 16 mg/day for 47 days and 5 others received 24 mg/day for 56 days. The observed decrease in cholinesterase activity reached a maximum 3 weeks after malathion was discontinued. Erythrocyte cholinesterase levels returned to baseline within 10 days and plasma cholinesterase leveled off at 93% of baseline within the same time period.

Hayes et al. (1390) found no decrease in blood cholinesterase following the dermal application of 28 g of 1.5% or 10% malathion dust 5 times weekly for 8-16 weeks. During the course of the experiment, burning and dermatitis were the only complaints noted. This study suggests that up to 2.5 g malathion/day can be safely applied to the skin. This is equal to an absorbed dose of 40 mg/kg for a 70 kg man.

Although depressive and schizophrenic behavior have been linked to exposure to organophosphate insecticides, including malathion (1391), no causal relationship has been established (1392).

50.3.3 Levels of Concern

The NAS (213) calculated a no-adverse-effect level for malathion in drinking water of 0.14 mg/L. An acceptable daily intake of 0.02 mg/kg body weight has also been established by the WHO for malathion (1668).

The USEPA has proposed an oral reference dose for malathion of 0.02 mg/kg/day (3744)

The NTP (1356) classifies malathion as presenting no evidence of carcinogenic activity in animals. IARC (1359) lists malathion as a category 3 carcinogen (i.e., insufficient evidence).

OSHA (3539) has set an 8-hour time-weighted-average of 10 mg/m^3 for total dust or 5 mg/m^3 for the respirable fraction of this compound. The ACGIH (3005) recommends a threshold limit value of 10 mg/m^3 for malathion.

50.3.4 Hazard Assessment

Malathion is an organophosphorus insecticide whose mode of action is the inhibition of cholinesterase enzymes. It is generally considered to be one of the least toxic to humans among this class of compounds. The major signs and symptoms of malathion intoxication include headaches, dizziness, weakness, tremors, sweating, blurred vision, chest tightness, diarrhea, salivation and lacrimation (1373).

Chronic toxicity information on this compound is surprisingly sparse. A two year study with rats indicated about 500 ppm malathion in the diet significantly decreased red-cell cholinesterase activity; reductions in growth and food intake were observed at 20,000 ppm (1376).

Two carcinogenicity studies conducted with both rats and mice were found to provide no evidence of carcinogenic activity (1354, 1355). Tests in bacteria and with mammalian and human cells in culture provide conflicting evidence of genotoxic activity for malathion (1360, 1361, 1364-1366, 3235, 3323, 3276).

Other studies noted no activity with malathion in a mouse dominant lethal test or in a test for chromosomal aberrations in mouse spermatogonia and bone marrow cells in vivo (1363, 1367). Mice treated cutaneously or intraperitoneally with malathion had significant increases in micronucleated bone marrow cells (3185) and humans exposed to malathion had significant evidence of chromosomal damage in lymphocytes examined immediately and one month after exposure (3725). Six months after exposure frequencies of chromosomal aberrations were approaching those of controls.

There is no evidence to suggest embryotoxic or teratogenic effects for malathion in studies conducted with rats (1159, 1370) and no significant effects on reproduction were noted in a two-generation rat study (1369). Studies with human volunteers indicate that ingestion of up to 16 mg of malathion daily for 47 days had no significant effect (1389). Available data suggest that relatively large quantities of malathion must be ingested for lethality. The human oral lethal dose is estimated to range from 400 to 1000 mg/kg (1300).

50.4 SAMPLING AND ANALYSIS CONSIDERATIONS

Determination of malathion concentrations in soil and water requires collection of a representative field sample and laboratory analysis. Care is required to prevent losses during sample collection and storage. Soil and water samples are collected in glass containers; extraction of samples should be completed within 7 days of sampling and analysis completed within 30-40 days. In addition to the targeted samples, quality control samples such as field blanks, duplicates, and spiked sample matrices may be specified.

EPA Method 8140 (63) is an approved procedure for the analysis of organophosphorus pesticides. Prior to analysis, samples are extracted at neutral pH with methylene chloride as the solvent using a separatory funnel or a continuous liquid-liquid extractor. An aliquot of the concentrated sample extract is injected onto a gas chromatographic (GC) column using a solvent flush technique. The GC column is programmed to separate the semivolatile organics; detection is achieved with either a thermionic detector operated in the phosphorus-sensitive mode or a flame photometric detector (FPD). The FPD is more selective for phosphorus than the thermionic detector. Compound identification may be confirmed by gas chromatography/mass spectrometry (GC/MS).

The same method is recommended for analysis in soil and waste samples. The procedure for solid samples differs from the aqueous procedure primarily in the preparation of the sample extract. Solid samples are extracted using either soxhlet extraction or sonication methods. Neat and diluted organic liquids may be analyzed by direct injection.

A detection limit for malathion using this method was not determined but would be in the range of 1-15 $\mu g/L$ for aqueous samples, 0.1-1 $\mu g/g$ for low level soil samples which have been sonicated and part-per-million (ppm) range for samples which have been directly injected.

Additional procedures for the determination of organophosphorus pesticides include thin-layer chromatography (3966, 3967) and indirect methods which rely no complexation with metallic species and subsequent measurement of the complex by atomic absorption spectrophotometry (AAS) (3964, 3965, 3968). Flow injection analysis with measurement of HPO emission at 528 nm has also been described for the rapid determination of insecticides extracted from water (3963). Relative retention data has been published for a large number of pesticides separated by GC under temperature programmed conditions to aid in the identification of unknowns (3969).

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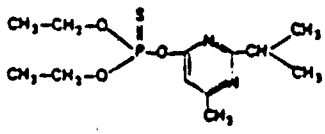
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COMMON SYNONYMS:	CAS REG.NO.: 333-41-5 FORMULA: $C_{12}H_{21}N_2O_3PS$ NIOSH NO: TF3325000	AIR W/V CONVERSION FACTOR at 25°C (12)
Diazide Diazinoe Dimpylate O,O-Diethyl-O-(6-methyl-2-(1-methyl-ethyl)-4-pyrimidinyl) phosphorothioate	STRUCTURE: 	12.44 mg/m³ ≈ 1 ppm; 0.08 ppm ≈ 1 mg/m³. MOLECULAR WEIGHT: 304.36

REACTIVITY	For compatibility classification purposes, Diazinon is considered to be in the reactivity group of organophosphates, phosphothioates and phosphodithioates. Such substances typically generate heat in reactions with alkali or alkaline earth metals; heat and toxic gases in reactions with mineral acids; and heat and possible explosions with caustics. Additionally reported are unknown but possibly hazardous reactions with azo or diazo compounds, hydrazines or organic peroxides or hydroperoxides. A maker reports that temperature above 53°C and strong alkaline materials should be avoided. Also noted is that the compound decompoces gradually in alkaline media to carbon dioxide, carbon monoxide, monothionotepp and diazoxon (507, 511).

PHYSICO-CHEMICAL DATA	• Physical State: Liquid (at 20°C)	(12)
	• Color: Colorless	(12)
	• Odor: Faint esterlike odor	(51)
	• Odor Threshold: No data	
	• Density: 1.1160 g/mL (at 20°C)	(51)
	• Freeze/Melt Point: Not pertinent	
	• Boiling Point: 84.00°C	(51)
	• Flash Point: Practically nonflammable; difficult to burn when pure	(13,60)
	• Flammable Limits: Not pertinent	(60)
	• Autoignition Temp.: Not pertinent	(60)
	• Vapor Pressure: 1.40E-04 mm Hg (at 20 deg°C)	(2)
	• Satd. Conc. in Air: 2.3000E+00 mg/m³ (at 20°C)	(1219)

PHYSICO-CHEMICAL DATA (Cont.)	• Solubility in Water: 4.00E+01 mg/L (at 20°C) (1118) • Viscosity: 3.201 cp (at 20°C) (60) • Surface Tension: 35 dyne/cm; (estim) (at 20°C) (60) • Log (Octanol-Water Partition Coeff.): 3.81 (1488) • Soil Adsorp. Coeff.: 4.40E+02 (1489) • Henry's Law Const.: 8.20E-07 atm · m³/mol (at 20°C) (964) • Bioconc. Factor: 3.10E+02 (estim) (37)
PERSISTENCE IN THE SOIL-WATER SYSTEM	Fairly immobile and non-persistent in soil water systems due to moderate sorption and moderate rate of degradation by hydrolysis and biodegradation. Typical half-life after soil application is 1-2 months. Photolytic degradation important for surface waters and soil surfaces.
PATHWAYS OF EXPOSURE	The primary pathway of concern from soil/ground-water systems is the migration of Diazinon® to ground water drinking water supplies. However, its potential for adsorption and degradation make the contamination of water supplies with Diazinon® less likely than other chemicals. Exposures through inhalation or bioaccumulation are not generally expected to be significant.
HEALTH HAZARD DATA	Signs and Symptoms of Short-term Human Exposure: (2, 45) Diazinon® is a cholinesterase inhibitor. Symptoms of exposure include weakness, headache, tightness in chest, blurred vision, non-reactive pinpoint pupils, salivation, sweating, nausea, vomiting, diarrhea, abdominal cramps and slurred speech. Convulsions and coma may also occur if poisoning is severe.

HEALTH HAZARD DATA	Acute Toxicity Studies: INHALATION: LC_{50} 1600 mg/m³ · 4 hr — Mouse ORAL: LD_{50} 85 mg/kg — Mouse TD_{Lo} 214 mg/kg — Child SKIN: LD_{50} 2750 mg/kg — Mouse Long-Term Effects: Headache, mental confusion, insomnia, muscular twitching Pregnancy/Neonate Data: Negative Genotoxicity Data: Negative Carcinogenicity Classification: IARC - No data NTP - Negative EPA - Group E (evidence of noncarcinogenicity for humans)

HANDLING PRECAUTIONS	Adequate ventilation • If respirator used, full facepiece type • Chemical goggles if there is probability of eye contact • Rubber, vinyl or nitrile gloves and protective clothing.

ENVIRONMENTAL AND OCCUPATIONAL STANDARDS AND CRITERIA

AIR EXPOSURE LIMITS:

Standards
- OSHA TWA (8-hr): 0.1 mg/m³ (skin)
- AFOSH PEL (8-hr TWA): 0.1 mg/m³; STEL (15-min): 0.3 mg/m³ (skin)

Criteria
- NIOSH IDLH (30-min): 5000 ppm
- NIOSH REL (10-hr TWA): Follow the current OSHA PELS.
- ACGIH TLV® (8-hr TWA): 0.1 mg/m³ (skin)

WATER EXPOSURE LIMITS:

Drinking Water Standards
MCLG: No data
MCL: No data

EPA Health Advisories and Cancer Risk Levels (3978)
The EPA has developed the following Health Advisories which provide specific advice on the levels of contaminants in drinking water at which adverse health effects would not be anticipated.

- 1-day (child): 20 µg/L
- 10-day (child): 20 µg/L
- longer-term (child): 5 µg/L
- longer-term (adult): 20 µg/L
- lifetime (adult): 0.6 µg/L

WHO Drinking Water Guideline
No information available.

EPA Ambient Water Quality Criteria
- Human Health (355)
  - No criterion established; Diazinon® is not a priority pollutant.
- Aquatic Life (355)
  - No criterion established; Diazinon® is not a priority pollutant.

REFERENCE DOSES: (3744)
ORAL: 0.09 µg/kg/day

REGULATORY STATUS (as of 01-MAR-89)

Promulgated Regulations

- Federal Programs

  Clean Water Act (CWA)
  Diazinon® is designated a hazardous substance. It has a reportable quantity (RQ) limit of 0.454 kg (347, 3764).

  Comprehensive Environmental Response Compensation and Liability Act (CERCLA)
  Diazinon® is designated a hazardous substance under CERCLA. It has a reportable quantity (RQ) limit of 0.454 kg (3766).

  Federal Insecticide, Fungicide and Rodenticide Act (FIFRA)
  EPA is canceling registrations and denying applications for Diazinon® use on golf courses and sod farms (1336). Pesticide registration standards for Diazinon® were issued by EPA in January, 1989 (3798). Tolerances for residues of Diazinon® in or on Chinese radishes are set at 0.1 ppm (314).

  Marine Protection Research and Sanctuaries Act (MPRSA)
  Ocean dumping of organohalogen compounds as well as the dumping of known or suspected carcinogens, mutagens or teratogens is prohibited except when they are present as trace contaminants. Permit applicants are exempt from these regulations if they can demonstrate that such chemical constituents are non-toxic and non-bioaccumulative in the marine environment or are rapidly rendered harmless by physical, chemical or biological processes in the sea (309).

  Occupational Safety and Health Act (OSHA)
  Employee exposure to Diazinon® shall not exceed an 8-hour time-weighted average (TWA) of 0.1 mg/m^3. Employee skin exposure to Diazinon® shall be prevented/reduced through the use of protective clothing and practices (3539).

  Hazardous Materials Transportation Act (HMTA)
  The Department of Transportation has designated Diazinon® as a hazardous material with a reportable quantity of 0.454 kg, subject to requirements for packaging, labeling and transportation (3180).

- State Water Programs

  ALL STATES
  All states have adopted EPA Ambient Water Quality Criteria and NPDWRs (see Water Exposure Limits section) as their promulgated state regulations, either by narrative reference or by relisting the specific numeric criteria. These states have promulgated additional or more stringent criteria:

  CALIFORNIA
  California has an action level of 14 µg/L (ppb) for Diazinon® in drinking water (3098).

KANSAS
Kansas has an action level of 0.63 µg/L for ground-water (3213).

NEW YORK
New York has set an MCL of 50 µg/L for Diazinon® in drinking water, a water quality standard of 0.7 µg/L for ground-water classed for drinking water supply, and an ambient water quality standard of 0.08 µg/L for fresh surface waters classed A, A-S, AA, AA-S, B, C, fishing, and fish propagation (3501, 3500).

OKLAHOMA
Oklahoma has set a nonenforceable Toxic Substance Goal of 0.024 ng/L for surface waters classed for public and private water supply (3534).

VERMONT
Vermont has a preventive action limit of 0.31 µg/L and an enforcement standard of 0.63 µg/L for Diazinon® in ground-water (3682).

Proposed Regulations

- Federal Programs
  No proposed federal regulations are pending.

- State Water Programs
  MOST STATES
  Most states are in the process of revising their water programs and proposing changes in their regulations which will follow EPA's changes when they become final. Contact with the state officer is advised. Changes are projected for 1989-90 (3683).

  MINNESOTA
  Minnesota has proposed a Recommended Allowable Limit (RAL) of 0.6 µg/L for drinking water (3451).

EEC Directives

Directive on Drinking Water (533)
The mandatory values for total pesticides in surface water treatment categories A1, A2 and A3 used or intended for abstraction of drinking water are 0.001, 0.0025 an 0.005 mg/L, respectively. There are no guideline values.

Directive Relating to the Quality of Water for Human Consumption (540)
The maximum admissible concentration for Diazinon® is 0.1 μg/L. The total maximum admissible concentration for pesticides and related products is 0.5 μg/L.

Directive on Ground-Water (538)
Direct discharge into ground-water (i.e., without percolation through the ground or subsoil) of organophosphorous compounds, organohalogen compounds and substances which may form such compounds in the aquatic environment, substances which possess carcinogenic, mutagenic or teratogenic properties in or via the aquatic environment and mineral oils and hydrocarbons is prohibited. Appropriate measures deemed necessary to prevent indirect discharge into ground-water (i.e., via percolation through ground or subsoil) of these substances shall be taken by member countries.

Directive on Bathing Water Quality (534)
When inspection of a bathing area shows that heavy metals, pesticides or cyanides may be present, concentrations should be checked by competent authorities.

Directive on the Discharge of Dangerous Substances (535)
Organohalogens, organophosphates, petroleum hydrocarbons, carcinogens or substances which have a deleterious effect on the taste and/or odor of human food derived from aquatic environments cannot be discharged into inland surface waters, territorial waters or internal coastal waters without prior authorization from member countries which issue emission standards. A system of zero-emission applies to discharge of these substances into ground-water.

Directive on Marketing and Use of Dangerous Substances (541)
Diazinon® may not be used in ornamental objects intended to produce light or color effects by means of different phases.

Directive on Classification, Packaging and Labeling of Pesticides (786) Diazinon® is listed as a Class II/a substance and is subject to packaging and labeling regulations.

Directive on the Classification, Packaging and Labeling of Dangerous Substances (787)
Diazinon® is classified as a toxic substance and is subject to packaging and labeling regulations.

EEC Directives - Proposed
Proposal for a Council Directive on the Dumping of Waste at Sea (1793)
EEC has proposed that the dumping of pesticides at sea be forbidden without prior issue of a special permit. The dumping areas shall be designated in the permit.

Resolution on a Revised List of Second-Category Pollutants (545)
Diazinon® is one of the second-category pollutants to be studied by the Commission in the programme of action of the European Communities on Environment in order to reduce pollution and nuisances in the air and water. Risk to human health and the environment, limits of pollutant levels in the environment, and determination of quality standards to be applied will be assessed.

51.1 MAJOR USES

Diazinon® is a popular insecticide among homeowners for its use in garden and lawn care. It is also widely used on fruits and vegetables and on forage and field crops. Diazinon® is used by professional exterminators to control cockroaches, silverfish, flies and fleas. It is also effective in the control of ticks and fleas on domestic animals and in the control of face fly larvae in livestock manure (54, 59).

51.2 ENVIRONMENTAL FATE AND EXPOSURE PATHWAYS

51.2.1 Transport in the Soil/Ground-water Systems

51.2.1.1 Overview

Diazinon® is expected to be relatively immobile in the soil ground water environment when present at low concentrations (dissolved in water). Bulk quantities of the liquid chemical (e.g., from a spill, heavy spray application, or improper disposal of excess formulations) could be transported down through the unsaturated zone. However, most studies have shown that normal application of Diazinon® sprays to soil surfaces do not result in transport of the chemical to any significant distance below the soil surface. Furthermore, as described later in this section, Diazinon® is readily susceptible to a number of degradation pathways (hydrolysis, photolysis, biodegradation) so that residuals from normal applications have fairly short half-lives (2-10 weeks) in the topsoil environment. The environmental persistence is strongly dependent upon temperature, soil pH, organic carbon content and microbiological activity, as well as other parameters. Under special conditions (e.g., no sunlight, low temperature, neutral soil pH, high soil organic carbon content), the half-life of Diazinon® in the environment could be quite long (months to years). Such conditions, in combination with high infiltration rates, could allow ground waters to be contaminated.

Diazinon® can act as a weak base, with protonation probably occurring first on the nitrogen in the '3' position (i.e., ortho to the ring methyl group). The value for pKa (1) is estimated to be 2.4 (1219) indicating that 50% of the chemical would be protonated at pH = 2.4, and 9% would be protonated at pH = 3.4, etc. The increased protonation at these low pH values would tend to significantly increase the chemical's solubility and mobility in the soil/ground-water system.

Environmental transport pathways for Diazinon® can be generally assessed by using an equilibrium partitioning model as shown in Table 51-1. These calculations predict the partitioning of low soil concentrations of Diazinon® among soil particles, soil water and soil air. The estimates for the unsaturated topsoil model show that while essentially all of the chemical (98.8%) is sorbed to the soil, a small amount (1.2%) is in solution and could be transported down with percolating waters.

TABLE 51-1
EQUILIBRIUM PARTITIONING CALCULATIONS FOR DIAZINON®
IN MODEL ENVIRONMENTS[a]

Soil Environment	Estimated Percent of Total Mass of Chemical in Each Compartment		
	Soil	Soil-Water	Soil-Air
Unsaturated topsoil at 20°C[b,c]	98.8	1.2	1.2E-06
Saturated deep soil[d]	65	35	-

a) Calculations based on Mackay's equilibrium partitioning model (34, 35, 36); see Introduction in Volume 1 for description of model and environmental conditions chosen to represent an unsaturated topsoil and saturated deep soil. Calculated percentages should be considered as rough estimates and used only for general guidance.
b) Utilized estimated soil sorption coefficient: K_{oc} = 440.
c) Henry's law constant taken as 8.2E-07 atm · m^3/mol at 20°C (964).
d) Used sorption coefficient K_p = 0.001 K_{oc}.

Negligible amounts of the chemical are predicted to be in the soil air and thus volatilization losses would be expected to be very small. In saturated, deep soils (containing no air and negligible soil organic carbon), the model predicts substantially more Diazinon® (35%) to be in the mobile ground-water phase.

Diazinon® has been used (in large quantities) as an insecticide for about 20 years. Many of the early studies on its transport and fate in the soil/ground-water system are described in references 1204-1208, 1211, 1216 and 1475.

51.2.1.2 Sorption on Soils

There appear to be relatively few studies focusing on the soil sorption properties of Diazinon®, in part because many studies have shown it to be readily degraded and thus not problematic with regard to its soil leaching potential.

Values of the equilibrium soil sorption constant, K_{oc}, for Diazinon® may be calculated from laboratory sorption data in two publications. An average K_{oc} of 445

is calculated from the data of Sharom et al. (1476) for three materials (a creek sediment, a sandy loam and a sand) while a value of 744 is obtained for an organic soil with 75.3% organic matter. A value of 417 is calculated from the data of Miles (1477) for a creek sediment. A K_{oc} value of 580 is cited by Laskowski et al. (1209) without any backup. All of these values are substantially lower (by a factor of 2 to 6) than would be predicted using correlations of K_{oc} with water solubility or with octanol-water partition coefficients. These values indicate that sorption of Diazinon® on topsoils (containing >0.1% organic carbon) is of moderate strength; i.e., most of the chemical will be sorbed to the soil, but not so strongly that leaching is prevented. As with all neutral organic chemicals, the extent of soil sorption is directly proportional to the soil organic carbon content. For low organic carbon soils (e.g., clays), the extent of sorption may also depend on other properties of the soil such as surface area, cation exchange capacity, and degree of hydration. Under certain conditions, Diazinon® can be sorbed into the interlayer spaces of montmorillonite clays (1212, 1478).

Other laboratory, field and modeling studies on the downward movement of soil-applied Diazinon® generally tend to support the conclusion that sorption is strong enough (in conjunction with degradation) to prevent contamination of ground-water aquifers (1215, 1216, 1479, 1480).

51.2.1.3 Volatilization from Soils

Diazinon® has a low vapor pressure (1.4E-04 mm Hg at 20°C (1204)) and a low Henry's Law constant (8.2E-07 atm m^3/mol at 20°C (1219). These values, coupled with the moderate extent of soil and sediment sorption of Diazinon®, imply that volatilization from soils (or surface waters) should not be an important transport pathway if water is present. However, experiments designed to measure Diazinon® losses from model soil pit and evaporation pond systems have shown that a significant fraction, and in some cases even a major fraction, of the chemical present may be lost to the air by volatilization (1217, 1218). Branham and Wehner (1479), who conducted microecosystem tests simulating Diazinon® application to turfgrass, concluded that volatilization accounted for a small amount of the chemical lost from the site of application. Jenkins et al. (1215) also showed that volatilization losses were small in lysimeter studies simulating land disposal of wastewater by spray irrigation. Volatilization losses from the surfaces of foliage or structures (e.g., after spray applications) could be substantially larger. Volatilization accounted for the loss of 86 percent of the Diazinon® on watch glasses over a 90 day period at 35°C; loss of 77.5 percent occurred within the first 15 days (1204).

51.2.2 Transformation Processes in Soil/Ground-water Systems

Diazinon® is susceptible to a number of degradation processes including hydrolysis, biodegradation and photolysis so that the chemical is not considered to be persistent in the environment.

Evidence for the photolytic degradation of Diazinon® (in surface waters or surfaces exposed to the light) is provided in references 1204, 1205 and 1485. Wolfe et al. (1205) concluded that the photolysis of Diazinon® by sunlight is a slow process, due principally to weak absorption of sunlight. The susceptibility of Diazinon® to indirect photolysis or free radical oxidation has not been investigated.

Data on the importance of hydrolysis in the environmental degradation of Diazinon® are provided in references 1204, 1205, 1207, 1216, 1221, 1475 and 1481-1484. In their 1976 review, Wolfe et al. (1205) concluded that hydrolysis of Diazinon® is very slow at pH values normally found in lakes and rivers (minimum half-life one month at 20°C), but that hydrolysis rates did increase with decreasing pH. The rate of hydrolysis, and subsequent environmental half-life, is strongly dependant on both pH and temperature as shown in Figures 51-1 and 51-2. Chapman and Cole (1207) summarize hydrolysis half-life measurements from several investigations, including their own, as shown in Table 51-2. Note that Diazinon® actually is most resistant to hydrolysis near pH 7.

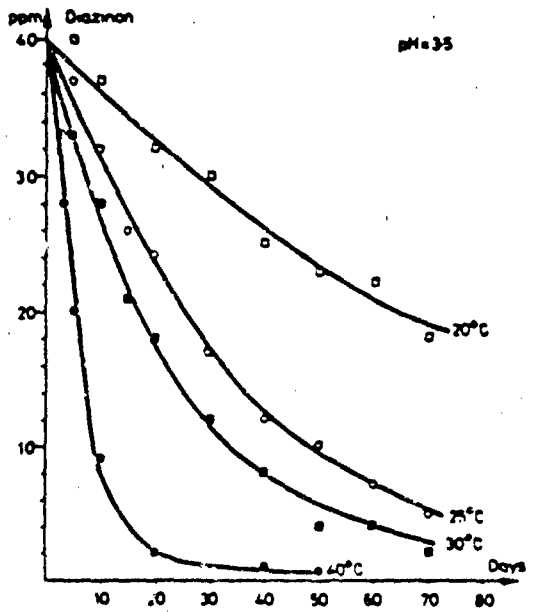


FIGURE 51-1

DECOMPOSITION OF DIAZINON® AS A FUNCTION OF TEMPERATURE

Source: Keeskes et al. (1475)

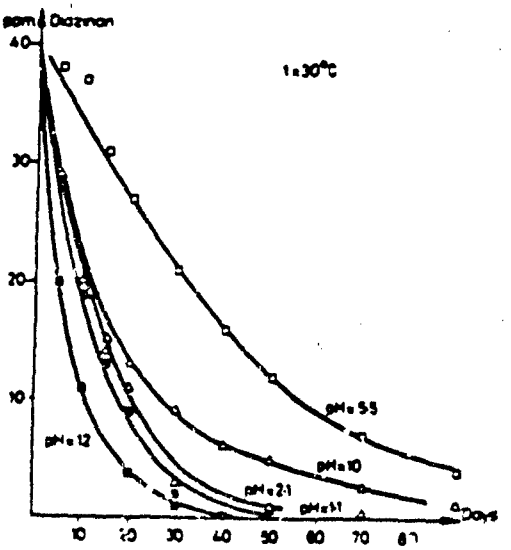


FIGURE 51-2

DECOMPOSITION OF DIAZINON® AS A FUNCTION OF pH

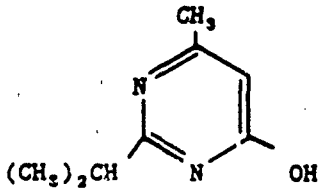
Source: Keeskes et al. (1475)

TABLE 51-2
HYDROLYSIS HALF-LIVES FOR DIAZINON® IN AQUEOUS SOLUTIONS AT TEMPERATURES NEAR 20°C

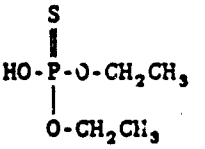
pH	No. of Data Points	Hydrolysis Half Life (weeks) Mean	Range
5	2	3	2 - 4
6	4	3.5	1 - 8
7	4	11	1 - 26
8	3	5	1 - 8

Source: Based on data in Chapman and Cole (1207); data are from 6 different publications.

From the above, it is clear that Diazinon® is subject to base and acid-catalyzed hydrolysis. Second-order alkaline hydrolysis rate constants of 5.6E-02/M/sec (20°C) and 2.4E-03/M/sec (27°C), and acid hydrolysis rate constants of 2.3E-02/M/sec (20°C) and 7.3E-02/M/sec (27°C), have been reported (1205). The principal initial hydrolysis products are 2-isopropyl-4- methyl-6-hydroxy pyrimidine (I) and O,O-diethyl phosphorothionic acid (II) (1204, 1205, 1481).



I



II

The effect of the presence of solids (sand, alumina, soil), humic acids, and other materials (e.g., cupric ions) on the hydrolysis of Diazinon® at various pHs has been investigated in several studies (1207, 1221, 1475, 1481, 1482, 1484) with some results being confusing or anomalous. To some extent the presence of solids may dampen the effect of pH on hydrolysis rates. It has been suggested that Diazinon® sorbed on soils is not susceptible to alkaline hydrolysis, but is susceptible to neutral hydrolysis (1484). The presence of cupric ions appears to catalyze the hydrolysis reaction (1205, 1221). The rate of hydrolysis decreases for Diazinon® when it is mixed in various technical formulations (e.g., dusts, oil solutions, emulsifiable concentrates) used for spray application (1481, 1482).

Studies on the biodegradation of Diazinon® are described in a number of reports (1204, 1211, 1216, 1223, 1224, 1475, 1479, 1486). The general conclusion is that under normal conditions Diazinon® is moderately biodegradable. Rao and Davidson (1210), using a variety of literature data from laboratory tests simulating aerobic conditions, estimated a mean biodegradation half life of 32-48 days.

Diazinon® can be the sole source of phosphorus for some species of microorganisms (1223). Acclimation appears to be important for biodegradation. Many studies have not adequately distinguished between the roles of abiotic hydrolysis and biologically mediated hydrolysis in the initial degradation steps yielding the two hydrolysis products mentioned above.

51.2.3 Primary Routes of Exposure from Soil/Ground-water Systems

The above discussion of fate pathways suggests that Diazinon® has a low volatility, is moderately sorbed to soil, and based on the bioconcentration factor calculated from its K_{ow}, Diazinon® has a moderate potential for bioaccumulation. These fate characteristics suggest several potential exposure pathways.

Volatilization of Diazinon® from a disposal site is not likely to represent an important exposure pathway under most conditions. Drinking water contamination resulting from the migration of Diazinon® with ground water may occur, although it is relatively immobile in soil and appears to be susceptible to a number of degradation pathways. This compound was not reported in Mitre's (83) compilation of compounds detected at the 546 National Priority List (NPL) sites. In addition, it has not been detected in any of the national drinking water surveys of ground water.

Discharges of Diazinon® to surface water from soil/ground-water systems would probably not represent significant sources of exposure due to Diazinon® degradability.

51.2.4 Other Sources of Human Exposure

Diazinon® has been registered as an insecticide and used on a wide variety of agricultural crops, domestic animals, lawns and gardens and household pests. As a result, consumers may be exposed through product use as well as the environment.

Diazinon® was detected in 48% of 123 air samples at 10 U.S. locations. The maximum concentration was 23 ng/m^3 and the mean concentration was 2.1 ng/m^3 (1242). These data suggest that inhalation may represent a common source of exposure, although at low levels.

NRC (213) stated that little information was available on the presence of Diazinon® in drinking water. Carey and Kutz (1242) reported that Diazinon® was found in 1.2% of the samples in the 1-14 National Surface Water Monitoring Program from 1976-1980 with a maximum value of 2.38 μg/L. It was also detected

infrequently in sediment over the same time period. It was found in 0.5% of the sediment samples with a maximum concentration of 7.1 µg/kg.

Due to its use on numerous agricultural crops, Diazinon® is commonly found in foods. It is included in the U.S. Food and Drug Administration's (FDA) Total Diet Study to determine the dietary intake of selected pesticides and other chemicals. The average daily intake for adults over the years 1976 - 1979 ranged from 0.004-0.010 µg/kg body weight/day. Average daily intakes for infants and toddlers over the same period ranged from 0.002-0.014 µg/kg/day. The largest source of exposure came from grain and cereal products, leafy vegetables and fruit.

The use of Diazinon® in home lawns and gardens can result in direct consumer exposure through both dermal and inhalation routes. Davis et al. (1559) examined the exposure to applicators of Diazinon®. They found that inhalation exposures ranged from 1.9-7.4 µg/hr over the period of application. Dermal exposures ranged from 5,500-29,000 µg/hr during the application period. The ranges were a function of the method of application, the area of application, and the amount of clothing worn. These data suggest that consumer exposures can be significant compared to other sources of exposure, although the frequency of exposure would be low.

51.3 HUMAN HEALTH CONSIDERATIONS

51.3.1 Animal Studies

51.3.1.1 Carcinogenicity

The National Cancer Institute (NCI) (1146) conducted a study of the carcinogenic effects of Diazinon® in F344 rats and B6C3F$_1$ mice. Rats were fed a diet containing 0, 400 or 800 ppm Diazinon® while mice were fed 0, 100 or 200 ppm Diazinon®. All animals were treated for 103 weeks. Low- and high-dose male rats and high-dose female rats showed signs of hyperactivity and all treated female rats exhibited signs of bloating, vaginal bleeding and vaginal discharge. The only clinical sign of Diazinon® toxicity in mice was hyperactivity. No dose-related trend in tumors was present in any of the treated rats or mice of either sex at incidences that could be clearly related to the administration of Diazinon® in the diet. Based on the data provided in this bioassay, the NCI concluded that Diazinon® was not carcinogenic for F344 rats or B6C3F$_1$ mice of either sex.

51.3.1.2 Genotoxicity

Diazinon® did not induce histidine revertants in all strains of Salmonella typhimurium tested (1108, 1143, 3468, 3187, 3816, 3860) nor did it induce tryptophan revertants in Escherichia coli WP2. (1108, 1143, 3468, 3187, 3860).

Strain D$_3$ of S. cerevisiae showed no recombinant activity of any kind when tested with Diazinon® (1143). Diazinon® also had no effect on unscheduled DNA

synthesis in strain WI-38 of human lung fibroblast cells (1143) or on sister chromatid exchange in Chinese hamster V79 cells (1109, 1144).

Significant increases in genotoxic response were observed when L5178 mouse lymphoma strains were tested without metabolic activation for mutation induction at the thymidine kinase locus (3439). Matsuoka et al. (3435) also observed significant increases in chromosomal aberrations in cultures of Chinese hamster lung cells, but only in the presence of metabolic activation.

Human cell cultures appear to need metabolic activation to respond to Diazinon® exposure. No increase in chromatid breaks or in sister chromatid exchanges was seen in human fibroblastic cells treated in culture with 0.06 or 0.03 mg/ml Diazinon® 40 to 48 hrs without metabolic activation (3611).

Sobti et al. (3666) observed a significant increase in sister chromatid exchanges when a cultures of LAZ-007 cells, (a human lymphoid cell line of B-cell origin) were treated with 20 µl Diazinon® for 48 hrs but only with metabolic activation.

51.3.1.3 Teratogenicity, Embryotoxicity and Reproductive Effects

The teratogenic effect of Diazinon® in rats was studied by Kimbrough and Gaines (1159). Pregnant Sherman rats were given a single intraperitoneal injection of 0, 100, 150 or 200 mg/kg Diazinon® on the 11th day of gestation. Fetuses were examined on day 20. Two of five dams treated with 200 mg/kg Diazinon® died before the experiment was completed. A high incidence of resorption (11 vs. 0.8 in control animals) was observed in this group. Of the six surviving fetuses, one had hydrocephalus (enlarged head due to fluid accumulation in the cranial vault), one had the first distal phalanx missing and one had ectomelia (incomplete or lack of development of long bones of the limbs). Dams injected with 150 mg/kg Diazinon® had a significantly reduced net weight gain (47 g vs. 82 g for controls). Fetal weights were also significantly reduced (2.56 g vs. 3.14 g in controls). No malformations were noted in the 150 mg/kg group. The only detrimental effect of the 100 mg/kg treatment was that 6 out of 50 fetuses exhibited a dilated renal pelvis. These results indicate that Diazinon® when injected intraperitoneally on the 11th day of gestation may induce malformations but only at doses toxic to the dams.

Diazinon® was not teratogenic in rabbits orally administered 7 mg/kg or 30 mg/kg during organogenesis (59). Similarly, no teratogenic effects were reported in hamsters fed 0.125 or 0.25 mg/kg Diazinon® during organogenesis. Cholinergic signs were seen in rabbits ingesting the high dose of Diazinon® and in all treated hamsters (59).

Similar to many organophosphate insecticides, Diazinon® has been shown to have a profound effect on avian embryogenesis when injected directly into chick eggs. Malformations are primarily skeletal, accompanied by a reduction in ribonucleotides in the embryo (1110, 1145, 3383). Diazinon® is therefore teratogenic in avian species, but in mammals it is teratogenic only at doses toxic to the dam.

51.3.1.4 Other Toxicologic Effects

51.3.1.4.1 Short-term Toxicity

Diazinon® is a cholinesterase inhibitor and typical signs of toxicity include vomiting, salivation, diarrhea, trembling, respiratory depression, cyanosis, pulmonary edema, convulsions and coma (45). The oral LD_{50} in the mouse is 85 mg/kg (59), while the dermal LD_{50} for this species is 2750 mg/kg (59). The inhalation LC_{50} in the mouse is listed as 1600 mg/m^3 for 4 hours (59).

Goats were given 0.5 or 5 mg/kg Diazinon® by gavage daily for 7 days, or a single dose of 150 or 700 mg/kg Diazinon®. There were no clinical signs of Diazinon® toxicity in the 0.5 or 5 mg/kg treatment groups. The goat given the single 150 mg/kg dose developed mild toxicosis in the form of constricted pupils during the first 24 hours of testing. The goat given the single dose of 700 mg/kg was hypersalivating within 1.5 hours of administration. By the second hour, CNS depression and abdominal pain were observed. Ataxia, periodic muscle tremors, disorientation, colic and groaning persisted and by the tenth hour the goat was unable to stand. Within two hours of treatment with appropriate drugs, the goat could stand and muscle tremors and hypersalivation ceased. Signs of toxicity began to recur by the 24th hour and treatment was again administered. The animal appeared fully recovered 6 days after the initial dose of Diazinon® (1112).

Intraperitoneal injection of a single dose of 100 mg/kg Diazinon® into male Wistar rats significantly inhibited both plasma and erythrocyte cholinesterase activity. Erythrocyte cholinesterase was inhibited more than plasma cholinesterase (18% activity by the 24th hour after dosing vs. 61% activity in plasma). Also, the Diazinon® content in the kidney was much greater than in the liver and brain. At 8 hours after administration, the Diazinon® content of the kidney was 500 times the level found in the liver and 11 times greater than the level found in the brain (1116).

Anesthetized dogs, cats, and guinea pigs were given a single iv dose of Diazinon® at 75 mg/kg. Acute edematous pancreatitis was observed in the dogs and guinea pigs as early as two hours after administration, but was not observed in the cats (a species that lacks pancreatic butyrylcholinesterase). Diazinon® treatment reduced serum butyrylcholinesterase (BuChE) in all three species. Serum amylase was elevated in the dogs but insignificantly decreased in the guinea pigs and cats. Pretreatment with atropine (0.2 mg/kg) prevented the acute pancreatitis. The authors concluded that the inhibition of pancreatic BuChE results in cholinergic hyperstimulation of pancreatic acinar cells and subsequent Diazinon®- induced acute pancreatitis (3229).

Husain et al (3312) reported tremors, convulsions, and lactic acidosis in female Wistar rats given a single dose (40 mg/kg ip) of Diazinon®. Two hours after administration the blood lactate levels were significantly increased, glycogen levels in the triceps and diaphragm were reduced, while glycogen phosphorylase activity in

these muscles was increased. These biochemical alterations and convulsant activity were prevented by prior administration of phenobarbitone sodium (40 mg/kg ip) suggesting that the lactic acidosis was due to glycogen depletion resulting from increased glycogen phosphorylase activity in the convulsing muscles (3215).

Coagulopathic effects were reported by Lox (3409) for female Sprague-Dawley rats receiving 157 ppm Diazinon® in the drinking water for 14 days. No significant effect on body weight gain or water intake was noted for the treated rats. Significant increases in prothrombin time, partial thromboplastin time and fibrinogen clotting time were noted for 14 day Diazinon® treated rats. Values for thromboplastin time, clotting factors II, VIII, X and XII, and hematocrit values were also abnormal one week after discontinuation of the Diazinon® treatment. It was noted that the Diazinon® concentration used was similar to that commonly used around the household.

Matin and Husain (3433) reported hyperglycemia, decreased cerebral acetylcholinesterase activity and glycogen content, and increased blood lactic acid levels in female rats receiving a single 40 mg/kg ip dose of Diazinon®. These biochemical alterations and the accompanying convulsions were abolished by diazepam (20 mg/kg ip) administered immediately after the Diazinon®. Activities of cerebral glycogen phosphorylase, phosphoglucomutase and hexokinase were also significantly increased, possibly indicating compensatory activity in response to the Diazinon®-induced stimulatory effects.

51.3.1.4.2 Chronic Toxicity

Davis and Holub (1158) investigated the effects of Diazinon® in male and female Wistar rats fed 0 or 25 ppm Diazinon® for 30 days. No clinical signs of toxicity were observed in any of the treated animals. A significant reduction in plasma cholinesterase activity was present in both male and female rats fed 25 ppm Diazinon®. Enzyme activity was 22-30% lower in the treated females than in the treated males. Erythrocyte acetylcholinesterase activity was also 13-17% lower in treated females than in treated males. Brain acetylcholinesterase activity was decreased in treated females, though not significantly over controls. However, this reduction in enzyme activity was statistically significant when compared to corresponding male enzyme levels. Davies and Holub concluded that female rats were more susceptible to Diazinon® than male rats when administered in the diet for a 30 day period.

Rats fed up to 1000 ppm technical Diazinon® in the diet for 4 weeks or 1000 ppm active Diazinon® as a wettable powder for 72 weeks exhibited no apparent gross signs of toxicity (12). In dogs, exposure to 9.3 mg/kg/day orally produced signs of toxicity after 5 weeks as well as complete cholinesterase inhibition. The animals had returned to normal 2 weeks after withdrawal of Diazinon® from the diet (12).

Diazinon® (1750 ppm by gavage) was shown to significantly reduce clotting time in rats after a short-term exposure (1111), which led Lox and Davis (1113) to

continue their investigation with an evaluation of clotting activity after long-term Diazinon® exposure. Female Sprague-Dawley rats were treated with 1 ppm Diazinon® in the drinking water for 6 months. Exposure to an extremely low level of Diazinon® continuously for 6 months produced no adverse effects on the blood clotting activity or hepatic morphology of female Sprague-Dawley rats.

51.3.2 Human and Epidemiologic Studies

51.3.2.1 Short-term Toxicologic Effects

The toxicity of Diazinon® is based on its ability to inhibit the activity of the cholinesterase enzymes (1115, 1158, 16). The resulting symptoms are similar to those found from excessive and continued stimulation of the CNS. Clinical signs include weakness, unsteadiness, blurred vision and a sense of constriction of the chest. This is usually followed by vomiting, abdominal cramps, diarrhea, salivation, profuse sweating, tremors of the extremities and difficulty breathing. Pinpoint and non-reactive pupils and cyanosis may occur as well as severe muscular fibrillations, convulsions and coma. Death primarily results from respiratory arrest due to the failure of the respiratory center, paralysis of the respiratory muscles or intense bronchoconstriction (5).

A fatal case of suicidal ingestion of Diazinon® was reported by Poklis et al. (1147). The victim was found dead along with a half empty bottle of pesticide containing 10% Diazinon® as the active ingredient. Post mortem examination revealed heavy, congested lungs and small intradermal and submucosal hemorrhages throughout the stomach and gastric mucosa and the grey and white matter of the brain. Diazinon® was detected in adipose tissue, bile, blood, brain, stomach contents, kidney and liver. It was estimated that the victim ingested 22 g of Diazinon® (i.e., 293 mg/kg bw). Plasma cholinesterase activity was found to be 0 Rappaport Units/ml (normal cholinesterase activity in adults is 40-80 Rappaport Units/ml plasma).

Another fatal Diazinon® suicide was reported by Heyndickx et al. (1148). Despite hospitalization, Diazinon® ingestion was not known to have occurred until the autopsy. The victim was admitted to the hospital with two severed radial veins. Despite seemingly successful treatment, the patient died a few hours later. Post mortem revealed edema of both lungs and an oily, green fluid in the stomach which analysis confirmed to be Diazinon®. The stomach and small intestines contained the majority of Diazinon® (756 mg% and 262 mg%, respectively). Brain, liver, kidney and lung tissue also revealed the presence of Diazinon®, but in much smaller amounts. Diazoxon, the more toxic metabolite, was not found in any tissue analyzed.

Wedin et al. (1114) reported an attempted case of suicide with renal involvement in addition to the general symptomatology usually observed. The patient was admitted to the hospital approximately one hour after ingesting 8 ounces of Diazinon® in water. The man was conscious and alert but was vomiting, had brachycardia (55 beats/minute) and hypoactive bowel sounds. Urine output, which was dark and cloudy, averaged 22 mL/hour. Urinalysis revealed moderate

unidentifiable crystals. Treatment was administered and all symptoms subsided, however, crystalluria persisted until the 9th day of hospitalization. In a review of this case study, Albright (1152) suggested that since no other cases of renal involvement have been reported for Diazinon®, the low urine output was most likely related to volume depletion rather than a nephrotoxic effect.

Two cases of dermal and respiratory exposure to Diazinon® and its breakdown products were reported by Soliman et al. (1153). Two men without gloves or masks were spraying a 60% diazinon-containing pesticide stored in tin containers. By noon time, one man complained of nausea and vomiting. He became weaker, the muscles of his limbs twitched and he had difficulty breathing. At the hospital he was given atropine sulfate and released the following morning without incident. The second man reported nausea and vomiting later that afternoon, but went home as usual. He continued to vomit, had burning eyes and blurred vision and had difficulty breathing. He became weaker and developed a severe headache which persisted for 3 days. Cholinesterase activity in both men was depressed by 38-58%. Subsequent blood tests from both victims revealed a substantial increase in plasma cholinesterase activity two weeks after the poisoning. The erythrocyte cholinesterase activity showed minimal improvement up to 18 days post-exposure. Analysis of the pesticide revealed the Diazinon® to have broken down, primarily into the major hydrolytic product, 2-isopropyl-4-methyl-6-hydroxypyrimidine along with small amounts of other transformation products such as O,O,O',O'-tetra-ethyldithiopyrophosphate and monothionotetraethylpyrophosphate. These organopyrophosphate products are the only known components of Diazinon® decomposition which are extremely toxic to humans (with the exception of diazoxon). The catalytic decomposition was thought to be caused by the tin containers used for storing the Diazinon®. Use of aluminum containers resulted in no reports of poisoning (1153).

An unusual case of Diazinon® poisoning was reported by Conyers and Goldsmith (1286). After washing sheep by hand with Diazinon® to prevent parasite infestation, a farmhand developed psychosis. Symptoms began within 6 hours and included insomnia and restlessness. The next morning the farmhand was confused, forgetful and apathetic. He was admitted to the hospital where the serum cholinesterase level was 0.9 IU/ml (the normal adult male serum cholinesterase range is 2.6-5.53 IU/ml). The patient recovered completely within 2 days with no evidence of mental confusion or memory loss. Six days after the poisoning incident his serum cholinesterase level was shown to increase to 2.0 IU/ml. Conyers and Goldsmith concluded that the cause of the farmhand's acute confusional psychosis was due to Diazinon® intoxication even though no other classical symptoms of Diazinon® toxicity manifested themselves.

Halle and Sloas (3260) reported the effects of dermal exposure of Diazinon® on a 58-year old man. One teaspoon of the compound had been applied to the genital area for the purpose of treating pubic lice. Thirty miniutes following exposure, the man experienced blurred vision and profuse diaphoresis, and nausea. Five to ten minutes later the man was unconscious and was salivating excessively. Plasma pseudocholinesterase level was 1 IU/ml. The patient recovered following pralidoxone

and atropine therapy. The authors emphasized the presence of four major criteria for diagnosis of organophosphate poisoning: (1) history of exposure, (2) clinical manifestations of cholinergic excess, (3) improvement with pralidoxone and atropine therapy, and (4) inhibition of blood cholinesterase activity.

A behavioral evaluation of 99 pest control workers who had experienced short-term, low-level exposure to Diazinon® indicated no adverse changes in neuro-behavioral function. The Diazinon® metabolite, diethylthiophosphate (DETP) was measured in pre- and post-shift urine samples from 46 workers applying Diazinon® and 56 non-applicators. Post-shift median DETP for these groups was 24 and 3 ppb, respectively. Median Diazinon® exposure for 19 workers was measured at 2.1 and 0.03 mg for applicators and non-applicators, respectively. The subjects tested were involved in a pest control program emphasizing personal protective equipment and direct supervision (3420).

51.3.2.2 Chronic Toxicologic Effects

Limited data are available on long-term human exposure to Diazinon® because, like other organophosphorus pesticides, it is an acutely poisonous agent and symptoms usually manifest between 1 and 24 hours post exposure.

Volunteers receiving 0.025-0.030 mg/kg Diazinon® for 32-34 days (route unspecified) showed no significant changes in plasma or erythrocyte cholinesterase activity (1150). A second study (1151) reported the results of 3 volunteers dosed (route unspecified) with 0.05 mg/kg Diazinon® daily for 5 days. After a 23-day period of no treatment, the subjects again received 0.05 mg/kg Diazinon® for 5 days. Plasma cholinesterase activity was inhibited by 60-65% compared with levels prior to testing. Three additional volunteers were then given 0.25 mg/kg Diazinon® daily for 43 days. Plasma cholinesterase activity was inhibited 15-20% (1151).

51.3.3 Levels of Concern

The OSHA standard for Diazinon® is an 8-hr TWA of 0.1 mg/m^3 with a notation of possible skin absorption.

The National Academy of Science calculated a no adverse effect level for Diazinon® in drinking water of 0.014 mg/L (54).

An acceptable daily intake of 0.002 mg/kg has been established for Diazinon® by WHO/FAO (54). The USEPA has proposed an oral Reference Dose of 0.09 µg/kg/day (3744). In drinking water, the USEPA has recommended a Lifetime Health Advisory of 0.6 µg/L (3978).

51.3.4 Hazard Assessment

The National Cancer Institute (1146) concluded Diazinon® was not carcinogenic for F344 rats fed up to 800 ppm in the diet or for B6C3F$_1$ mice fed up to 200 ppm in the diet for two years. Genotoxicity tests with this compound produce conflicting results.

A few malformed fetuses (3 of 6 survivors) were reported for rats injected with 200 mg/kg Diazinon® intraperitoneally during gestation; however, this dose was lethal to 2 of 5 dams. Studies in rabbits and hamsters administered Diazinon® orally gave no indications of teratogenic effects (59).

Diazinon® is a cholinesterase inhibitor. Typically signs of toxicity include vomiting, salivation, diarrhea, trembling, respiratory depression, cyanosis, pulmonary edema, convulsions and coma (45). Long -term exposure of laboratory animals produced no gross signs of toxicity, alterations in growth or pathology at autopsy (12) but did result in significant reductions in plasma cholinesterase activity.

Limited data are available with regard to chronic human exposure to Diazinon® due to the acute toxic nature of Diazinon®. One report did note, however, that no adverse effects other than inhibition of plasma cholinesterase by 15-20% were recorded for human volunteers given 0.25 mg/kg Diazinon® daily for 43 days. The route of administration was not specified (1151).

51.4 SAMPLING AND ANALYSIS CONSIDERATIONS

Determination of Diazinon concentration in soil and water requires collection of a representative field sample and laboratory analysis. Care is required to prevent losses during sample collection and storage. Soil and water samples are collected in glass containers; extractions of samples should be completed within 7 days of sampling and analysis completed within 30-40 days. In addition to the targeted samples, quality control samples such as field blanks, duplicates, and spiked matrices may be specified.

EPA Method 8140 (63) is an approved procedure for the analysis of Diazinon® in aqueous samples. Prior to analysis, samples are extracted at neutral pH with methylene chloride as the solvent using a separatory funnel or a continuous liquid-liquid extractor. An aliquot of the concentrated sample extract is injected onto a gas chromatographic (GC) column using a solvent flush technique. The GC column is programmed to either a thermionic detector operated in the phosphorus sensitive mode or a flame photometric detector (FPD). The FPD is more selective for phosphorus than the thermionic detector. Compound identification may be confirmed by gas chromatography/mass spectrometry (GC/MS).

The same method is recommended for Diazinon® analysis in soil and waste samples. The procedure for solid samples differ from the aqueous procedure primarily in the preparation of the sample extract. Solid samples are extracted using

either soxhlet extraction or sonication methods. Neat and diluted organic liquids may be analyzed by direct injection.

In addition to these methods, Diazinon® has also been determined in water by GC using an electron capture detector (3491). A high peformance liquid chromatographic procedure using a reversed-phase column and absorbance detection at 220 nm provides a limit of detection at 0.5 μg/ml (3426). Isotope dilution GC/MS has also been used for water and soil samples (3404).

Typical Diazinon® detection limits that can be obtained in wastewaters and non-aqueous samples (wastes, soils, etc.) are shown below. The actual detection limit achieved in a given analysis will vary with instrument sensitivity and matrix effects.

Aqueous Detection Limit	Non-Aqueous Detection Limit
6.0 μg/L (Method 8140)	0.4 μg/g (Method 8140)

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Note: The nonsequential numbers of the references reflect the order of references as they appear in the master bibliography.

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Arochlor® 1016		
COMMON SYNONYMS: Chlorodiphenyl (41% Cl) PCB 1016	FORMULA OF MAJOR COMPONENTS: $C_{12}H_8Cl_2$ 20.0% $C_{12}H_7Cl_3$ 57.0% $C_{12}H_6Cl_4$ 21.0%	CAS REG. NO.: 12674-11-2 NIOSH NO.: TQ1351000 MOLECULAR WEIGHT: 258.00 (average)

PHYSICO-CHEMICAL DATA	• Physical State: Liquid, oily (at 20°C)	(1457)
	• Color: Clear	(1457)
	• Odor: Mild hydrocarbon	(1457)
	• Odor Threshold: No data	
	• Density: 1.4400 g/mL (at 30°C)	(54)
	• Freeze/Melt Point: -18.89°C	(2)
	• Boiling Point: 340.00 to 375.00°C	(54)
	• Flash Point: Relatively nonflammable	(67,508)
	• Flammable Limits: No data	
	• Autoignition Temp.: Can be incinerated at high temperatures	(12,54)
	• Vapor Pressure: 4.00E-04 mm Hg (at 25°C)	(10)
	• Satd. Conc. in Air: 5.60 mg/m³ (ADL estim) (at 20°C)	
	• Solubility in Water: 2.20E-01 to 9.10E-01 mg/L (at 25°C)	(1583,1586, 1589)
	• Viscosity: No data	
	• Surface Tension: No data	
	• Log (Octanol-Water Partition Coeff.): 5.30 to 5.60	(29)
	• Soil Adsorp. Coeff.: 1.00E+05 approx.	(611)
	• Henry's Law Const.: 3.20E-04 atm · m³/mol (at 25°C)	(31)
	• Bioconc. Factor: 1.00E+04 to 1.00E+06	(10)

Aroclor® 1242		
COMMON SYNONYMS: Chlorodiphenyl (42% Cl) PCB 1242	FORMULA OF MAJOR COMPONENTS: $C_{12}H_7Cl_3$ 49.0% $C_{12}H_6Cl_4$ 25.0% $C_{12}H_5Cl_5$ 8.0% $C_{12}H_4Cl_2$ 16.0%	CAS REG. NO.: 53469-21-9 NIOSH NO.: TQ1356000 MOLECULAR WEIGHT: 266.00 (average)

PHYSICO-CHEMICAL DATA	• Physical State: Liquid (at 20°C)	(46)
	• Color: Straw; dark brown	(46)
	• Odor: Mild hydrocarbon	(2)
	• Odor Threshold: No data	
	• Density: 1.3800 to 1.3900 g/mL (at 20°C)	(12)
	• Freeze/Melt Point: -19.00°C	(38)
	• Boiling Point: 325.00 to 366.00°C	(38)
	• Flash Point: Relatively nonflammable	(67,508)
	• Flammable Limits: No data	
	• Autoignition Temp.: Can be incinerated at high temperatures	(12,54)
	• Vapor Pressure: 4.00E-04 mm Hg (at 25°C)	(10)
	• Satd. Conc. in Air: 5.80 mg/m^3 (ADL estim) (at 20°C)	
	• Solubility in Water: 2.00E-01 to 7.00E-01 mg/L (at 25°C)	(1583,1586, 1589)
	• Viscosity: No data	
	• Surface Tension: No data	
	• Log (Octanol-Water Partition Coeff.): 5.30 to 6.10	(29)
	• Soil Adsorp. Coeff.: 1.00E+05 approx.	(611)
	• Henry's Law Const.: 3.40E-04 atm · m^3/mol (at 25°C)	(1571)
	• Bioconc. Factor: 1.00E+04 to 1.00E+06	(10)

Aroclor® 1254		
COMMON SYNONYMS: Chlorodiphenyl (54% Cl) PCB 1254	FORMULA OF MAJOR COMPONENTS: $C_{12}H_5Cl_5$ 48.0% $C_{12}H_4Cl_4$ 23.0% $C_{12}H_3Cl_7$ 6.0% $C_{12}H_4Cl_4$ 21.0%	CAS REG. NO.: 11097-69-1 NIOSH NO.: TQ1360000 MOLECULAR WEIGHT: 328.00 (average)

PHYSICO-CHEMICAL DATA	• Physical State: Liquid, viscous (at 20°C)	(38)
	• Color: Pale yellow	
	• Odor: Mild hydrocarbon	(38)
	• Odor Threshold: No data	
	• Density: 1.4700 to 1.4900 g/mL (at 90°C)	(12)
	• Freeze/Melt Point: 10.00°C pour point	(38)
	• Boiling Point: 365.00 to 390.00°C	(38)
	• Flash Point: Relatively nonflammable	(67,508)
	• Flammable Limits: No data	
	• Autoignition Temp.: Can be incinerated at high temperatures	(12,54)
	• Vapor Pressure: 6.00E-05 mm Hg (at 20°C)	(38)
	• Satd. Conc. in Air: 1.10 mg/m^3 (at 20°C) (ADL estim)	
	• Solubility in Water: 1.20E-02 to 7.00E-02 mg/L (at 20°C)	(10,1583)
	• Viscosity: No data	
	• Surface Tension: No data	
	• Log (Octanol-Water Partition Coeff.): 5.60 to 8.00	(29)
	• Soil Adsorp. Coeff.: 1.00E+05 to 1.00E+07	(611)
	• Henry's Law Const.: 2.80E-04 $atm \cdot m^3/mol$ (at 20°C)	(1571)
	• Bioconc. Factor: 1.00E+04 to 1.00E+06	(10)

Aroclor® 1260		
COMMON SYNONYMS: Chlorodiphenyl (60% Cl) Clophen A60 PCB 1260 Phenoclor DP6	FORMULA OF MAJOR COMPONENTS: $C_{12}H_4Cl_6$ 38.0% $C_{12}H_3Cl_7$ 41.0% $C_{12}H_2Cl_8$ 8.0% $C_{12}H_1Cl_9$ 12.0%	CAS REG. NO.: 11096-82-5 NIOSH NO.: TQ1362000 MOLECULAR WEIGHT: 376.00 (average)

PHYSICO-CHEMICAL DATA	• Physical State: Liquid (at 20°C)	(23)
	• Color: Colorless	(23)
	• Odor: No data	
	• Odor Threshold: No data	
	• Density: 1.4400 g/mL (at 30°C)	(54)
	• Freeze/Melt Point: No data	
	• Boiling Point: 340.00 to 375.00°C	(54)
	• Flash Point: Relatively nonflammable	(67,508)
	• Flammable Limits: No data	
	• Autoignition Temp.: Can be incinerated at high temperatures	(12,54)
	• Vapor Pressure: 4.00E-05 mm Hg (at 25°C)	(10)
	• Satd. Conc. in Air: 8.00 E-01 mg/m^3 (ADL estim) (at 20°C)	
	• Solubility in Water: 2.70E-03 mg/L (at 20°C)	(10)
	• Viscosity: No data	
	• Surface Tension: No data	
	• Log (Octanol-Water Partition Coeff.): 6.10 to 9.30	(29)
	• Soil Adsorp. Coeff.: 1.00E+05 to 1.00E+09	(611)
	• Henry's Law Const.: 3.40E-04 atm · m^3/mol (at 20°C)	(1571)
	• Bioconc. Factor: 1.00E+04 to 1.00E+06	(10)

REACTIVITY	Aroclor® compounds are generally considered halogenated organic compounds for compatibility classification purposes. Reactions of such materials with cyanides, mercaptans or other organic sulfides typically generate heat, while those with amines, azo compounds, hydrazines, caustics or nitrides commonly evolve heat and toxic or flammable gases. Reactions with oxidizing mineral acids may generate heat, toxic gases and fires. Reactions with alkali or alkaline earth metals, certain other chemically active elemental metals like aluminum, zinc or magnesium, organic peroxides or hydroperoxides, strong oxidizing agents or strong reducing agents typically result in heat generation and explosions and/or fires. PCBs are specifically known to react exothermally with liquid chlorine. Photolysis in sunlight causes various degradative reactions (12, 505, 511).
PERSISTENCE IN THE SOIL-WATER SYSTEM	Aroclor® 1016, 1242, 1254 and 1260 are expected to be highly immobile in the soil/ground-water system due to rapid and strong sorption. In the absence of organic solvents, leaching is minimal; the presence of organic solvents (e.g., chlorobenzenes) may significantly increase mobility. Volatilization is expected to be slow, but may be a significant long-term transport process. Photolytic and biological degradation of PCBs may occur in the soil/ground-water environment but are not expected to be rapid. In general, the higher chlorinated biphenyls are less mobile and more persistent than the lower chlorinated species.
PATHWAYS OF EXPOSURE	Although they are generally strongly sorbed, the primary pathway of concern from a soil/ground-water system is the migration of PCBs to groundwater drinking water supplies. Inhalation may be an important exposure pathway in some cases. Fish contamination and consumption may occur upon release to surface waters.

HEALTH HAZARD DATA	Signs and Symptoms of Short-term Human Exposure: (46) Systemic effects include anorexia, nausea, edema of the face and hands, and abdominal pain. A burning sensation to the skin and eyes as well as eye discharge are also common. Acute Toxicity Studies: (Aroclor® 1016) ORAL: LD_{50} 2300 mg/kg — Rat (1178) (Aroclor® 1242) SKIN: LD_{50} 8650 mg/kg — Rabbit (1178) ORAL: LD_{50} 794-1269 mg/kg — Rat (1178) (Aroclor® 1254): ORAL: LD_{50} 1300-2000 mg/kg — Rat (1178) (Aroclor® 1260): SKIN: LD_{Lo} 1300-2000 mg/kg — Rabbit (59) ORAL: LD_{50} 4000-10000 mg/kg — Rat (59) Aroclor 1016 Long-Term Effects: Chloracne, liver injury Pregnancy/Neonate Data: Reduced reproductive capacity Genotoxicity Data: Conflicting data Carcinogenicity Classification: IARC - Group 2A (probably carcinogenic to humans) NTP - No data EPA - Group B2 (as a mixture); (probable human carcinogen; sufficient evidence in animals, insufficient evidence in humans)

HEALTH HAZARD DATA (Cont.)	Aroclor® 1242 Long-Term Effects: Chloracne, liver injury Pregnancy/Neonate Data: Reduced reproductive capacity Genotoxicity Data: Conflicting data Carcinogenicity Classification: IARC - Group 2A (probably carcinogenic to humans) NTP - No data EPA - Group B2 (as a mixture); (probable human carcinogen; sufficient evidence in animals, insufficient evidence in humans) Aroclor® 1254 Long-Term Effects: Chloracne, liver injury Pregnancy/Neonate Data: Reduced reproductive capacity Genotoxicity Data: Conflicting data Carcinogenicity Classification: IARC - Group 2A (probably carcinogenic to humans) NTP - Equivocal evidence of carcinogenicity in F344 rats EPA - Group B2 (as a mixture); (probable human carcinogen; sufficient evidence in animals insufficient evidence in humans) Aroclor® 1260 Long-Term Effects: Chloracne, liver injury Pregnancy/Neonate Data: Reduced reproductive capacity Genotoxicity Data: Conflicting data Carcinogenicity Classification: IARC - Group 2A (probably carcinogenic to humans) NTP - No data EPA - Group B2 (as a mixture); (probable human carcinogen; sufficient evidence in animals)

HANDLING PRECAUTIONS (38)	Aroclor® 1016 and 1242 Vapor concentrations of 1-10 mg/m³: any supplied-air respirator with a full facepiece, helmet or hood or any self-contained breathing apparatus with full facepiece • >10 mg/m³: self-contained breathing apparatus with a full facepiece operated in the pressure-demand or other positive pressure mode or a combination respirator which includes a Type C supplied-air respirator with full facepiece operated in pressure-demand or other positive pressure or continuous flow mode and an auxiliary self-contained breathing apparatus operated in pressure-demand or other positive pressure mode • Impervious clothing, gloves, face shields (8-inch minimum) and other appropriate protective clothing to prevent possible skin contact • Splash-proof safety goggles if eye contact is possible. Aroclor® 1254 and 1260 Vapor concentrations of 0.5-5 mg/m³: any supplied-air respirator with a full facepiece, helmet or hood or any selfcontained breathing apparatus with full facepeice • >5 mg/m³: self-contained breathing apparatus with a full facepiece operated in the pressure-demand or other positive pressure mode or a combination respirator which includes a Type C supplied-air respirator with full facepiece operated in pressure-demand or other positive pressure or continuous flow mode and an auxiliary self-contained breathing apparatus operated in pressure-demand or other positive pressure mode • Impervious clothing, gloves, face shields (8-inch minimum) and other appropriate protective clothing to prevent possible skin contact • Splash-proof safety goggles if eye contact is possible.

ENVIRONMENTAL AND OCCUPATIONAL STANDARDS AND CRITERIA

AIR EXPOSURE LIMITS:

Standards
- OSHA TWA (8-hr): chlorodiphenyl 42% chlorine: 1 mg/m³; 54% chlorine: 0.5 mg/m³ (skin)
- AFOSH PEL (8-hr TWA): chlorodiphenyl 42% chlorine: 1 mg/m³; 54% chlorine: 0.5 mg/m³ (skin); STEL (15-min); 3 mg/m³ and 1.5 mg/m³, respectively

Criteria
- NIOSH IDLH (30-min): chlorodiphenyl 42% chlorine & 54% chlorine: NIOSH has recommended that the substance be treated as a potential human carcinogen.
- NIOSH REL: 1 µg/m³ (the minimum reliably detectable concentration using the recommended sampling and analytical methods)
- ACGIH TLV® (8-hr TWA): chlorodiphenyl 42% chlorine: 1 mg/m³; 54% chlorine: 0.5 mg/m³ (skin)

WATER EXPOSURE LIMITS:

Drinking Water Standards (3883)
MCLG: 0 µg/L (proposed)
MCL : 0.5 µg/L (proposed)

EPA Health Advisories and Cancer Risk Levels (3742)
The EPA has developed the following Health Advisories which provide specific advice on the levels of contaminants in drinking water at which adverse health effects would not be anticipated.

- longer-term (child): 1 µg/L
- longer-term (adult): 4 µg/L
- 1E-04 cancer risk: 0.5 µg/L

WHO Drinking Water Guideline
No information available.

EPA Ambient Water Quality Criteria
- Human Health (355)
  - Based on ingestion of contaminated water and aquatic organisms, (1E-05, 1E-06, 1E-07 cancer risk), 0.79 ng/L, 0.079 ng/L, 0.0079 ng/L total PCBs.
  - Based on ingestion of contaminated aquatic organism only, (1E-05, 1E-06, 1E-07 cancer risk), 0.79 ng/L, 0.079 ng/L, 0.0079 ng/L total PCBs.

ENVIRONMENTAL AND OCCUPATIONAL STANDARDS AND CRITERIA (Cont.)

- Based on ingestion of contaminated drinking water alone, (1E-05, 1E-06, 1E-07 cancer risk), 126 ng/L, 12.6 ng/L, 1.26 ng/L total PCBs.

- Aquatic Life (355)
  - Freshwater species
    To protect freshwater aquatic life the criterion is 0.014 µg/L total PCBs as a 24-hour average.

  - Saltwater species
    To protect saltwater aquatic life, the criterion is 0.030 µg/L total PCBs as a 24-hour average.

REFERENCE DOSES:
No reference dose available.

REGULATORY STATUS (as of 01-MAR-89)

Promulgated Regulations
- Federal Programs
  Clean Water Act (CWA)
  Under the toxic pollutant effluent standards, polychlorinated biphenyls (PCBs) are prohibited in any discharge from any manufacturer of PCBs, electrical capacitors or electrical transformers (850). PCBs are designated hazardous substances. They have a reportable quantity (RQ) of 4.54 kg (347, 3764). They are also listed as toxic pollutants, subject to general pretreatment regulations for new and existing sources, and effluent standards and guidelines (351, 3763). Effluent limitations specific to this chemical group have been set in the following point source categories: electroplating (3767), steam electric power generating (3802), pulp, paper, and paperboard (898) and metal finishing (3768). Limitations vary depending on the type of plant and industry.

  Safe Drinking Water Act (SDWA)
  PCBs are on the list of 83 contaminants required to be regulated under the SDWA of 1974 as amended in 1986 by January, 1991 (3781). In states with an approved Underground Injection Control program, a permit is required for the injection of PCB-containing wastes designated as hazardous under RCRA (295).

Resource Conservation and Recovery Act (RCRA)
PCBs are listed as hazardous waste constituents (3783). PCBs are subject to land disposal restrictions when their concentration as hazardous constituents of certain wastewaters exceeds designated levels (3785). Solid wastes containing concentrations of PCBs equal to or greater than 10 mg/kg (dry weight) must be incorporated into soil when it is to be applied to land used for producing animal feed. Incorporation of the waste into the soil is not required if it is assured that the PCB content is less than 0.2 mg/kg (actual weight) in animal feed or less than 1.5 mg/kg (fat basis) in milk (1237). Effective July 8, 1987, the land disposal of untreated liquid hazardous wastes containing PCBs at concentrations greater than or equal to 50 ppm is prohibited. Effective August 8, 1988, the underground injection into deep wells is prohibited (3786). EPA requires that liquid hazardous wastes containing PCBs in concentrations greater than or equal to 50 ppm but less than 500 ppm must be incinerated or burned in high efficiency boilers in accordance with requirements outlined under the Toxic Substances Control Act at 40CFR761.70 and 761.60. Liquid hazardous wastes with PCBs in excess of 500 ppm must be incinerated (3782). PCBs are on EPA's ground-water monitoring list. EPA requires that all hazardous waste treatment, storage, and disposal facilities monitor their ground-water for chemicals on this list when suspected contamination is first detected and annually thereafter (3775).

Toxic Substances Control Act (TSCA)
The use of PCBs is prohibited except when used in a totally enclosed manner which ensures that any exposure of human beings or the environment will be insignificant. EPA may authorize the use of PCBs in a manner other than totally enclosed if that use will not present an unreasonable risk of injury to health or the environment. PCBs at concentrations of 50 ppm or greater must be disposed of in an incinerator. Numerous exceptions to this disposal requirement are outlined in 40CFR761.60. When storage is desired prior to disposal, PCBs at concentrations of 50 ppm or greater shall be stored in a facility which complies with 40CFR761.65 (1769). All PCB spills must be cleaned up in accordance with TSCA's Spill Cleanup Policy as outlined in 40CFR761. All PCB spills of 10 pounds or more, or spills directly contaminating surface waters, sewers, drinking water, grazing lands, or vegetable gardens must be reported to the EPA regional office within 24 hours after discovery and cleaned up in accordance with measures outlined in 40CFR761 (3778). Installation of PCB transformers in or near commercial buildings is banned as of October 1, 1985, except in certain emergency situations or for purposes of reclassification. EPA is allowing the installation of retrofilled PCB transformers until October 1, 1990. The use of lower secondary voltage network PCB transformers located in sidewalk vaults near commercial buildings is prohibited as of October 1, 1993 (3790).

Comprehensive Environmental Response, Compensation and Liability Act (CERCLA)
PCB compounds are designated hazardous substances under CERCLA. They have a reportable quantity (RQ) limit of 4.54 kg. Reportable quantities have also been issued for RCRA hazardous waste streams containing PCBs, but these depend upon the concentrations of the chemicals in the waste stream (3766). Under SARA Title III Section 313, manufacturers, processors, importers, and users of PCBs must report annually to EPA and state officials their releases of this chemical to the environment (3787). Under the National Contingency Plan, all spills involving 10 pounds or more of PCB material must be reported to the National Response Center (1-800-424-8802) (3778).

Marine Protection Research and Sanctuaries Act (MPRSA)
Ocean dumping of organohalogen compounds as well as the dumping of known or suspected carcinogens, mutagens or teratogens is prohibited except when they are present as trace contaminants. Permit applicants are exempt from these regulations if they can demonstrate that such chemical constituents are non-toxic and non-bioaccumulative in the marine environment or are rapidly rendered harmless by physical, chemical or biological processes in the sea (309).

Occupational Safety and Health Act (OSHA)
Exposure to chlorodiphenyl (54% chlorine) (PCB) in any 8-hour work-shift of a 40-hour work-week shall not exceed an 8-hour time-weighted average of 0.5mg/m^3. Exposure of chlorodiphenyl (42% chlorine) (PCB) in any 8-hour work-shift of a 40-hour work-week shall not exceed 1.0mg/m^3. Both compounds have skin designations (3539).

Hazardous Materials Transportation Act (HMTA)
The Department of Transportation has designated PCBs as hazardous materials with a reportable quantity of 4.54 kg, subject to requirements for packaging,labeling and transportation (3180).

Food, Drug and Cosmetic Act (FDCA)
The temporary tolerances for PCB residues are as follows: 1.5 ppm in milk and manufactured dairy products (fat basis) 3 ppm in poultry (fat basis) 0.3 ppm in eggs 0.2 ppm in finished animal feed for food producing animals and in infant and junior foods 2 ppm in animal feed components of animal origin and in the edible portion of fish and shellfish 10 ppm in paper food-packaging material (1404) A number of restrictions are outlined in 21CFR109.15 on the industrial uses of PCBs in establishments manufacturing food-packaging materials, to preclude the accidental PCB contamination of food-packaging materials (3799).

- State Water Programs
  ALL STATES
  All states have adopted EPA Ambient Water Quality Criteria and NPDWRs (see Water Exposure Limits section) as their promulgated

state regulations, either by narrative reference or by relisting the specific numeric criteria. These states have promulgated additional or more stringent criteria:

ARKANSAS
Arkansas has a chronic toxicity criterion of 0.014 μg/L (24-hour average) and an acute toxicity criterion of 2 μg/L (never to exceed) for the protection of aquatic organisms from PCBs in surface waters (3587).

CONNECTICUT
Connecticut has an action level of 1 μg/L for PCBs in drinking water (3138).

FLORIDA
Florida has a water quality criterion of 0.001 μg/L for PCBs in Class I, II, and III surface waters (3220).

KANSAS
Kansas has an action level of 0.05 μg/L for total PCBs in ground-water (3213).

MARYLAND
Maryland sets an upper limit of 0.001 μg/L for PCBs in surface water (3684).

MISSOURI
Missouri has a surface water quality criterion for PCBs of 0.0079 ng/L for the protection of aquatic life (3457).

NEW HAMPSHIRE
New Hampshire has set an MCL for PCBs in drinking water of 1 μg/L for one month (assumes a 10 kg child who drinks one liter of water per day) (3710).

NEW JERSEY
New Jersey has set an MCL of 0.5 μg/L for PCBs in drinking water (3497).

NEW YORK
New York has an MCL of 1 μg/L for PCBs in drinking water and a water quality standard of 0.1 μg/L for PCBs in ground-water that is classed for drinking water supply (3501). New York has also set ambient water quality standards for PCBs in surface water: 0.01 μg/L for drinking water supply waters, 0.001 μg/L for water Classes A, A-S, AA, AA-S, B, C, D, SA, SB, SC and SD (3500).

NORTH CAROLINA
North Carolina has a water quality standard for PCBs of 0.001 μg/L for fresh surface waters and tidal salt waters (3681).

NORTH DAKOTA
North Dakota has a surface water quality standard of 0.15 μg/L for PCBs in Class I, IA, II, and III streams (3512).

OKLAHOMA
Oklahoma has a surface water quality standard of 0.3 µg/L for PCBs in waters designated for fish and wildlife propagation (3534).

SOUTH DAKOTA
South Dakota has a water quality standard of 0.001 µg/L for PCBs in surface and ground-waters (3672, 3671).

VERMONT
Vermont has a preventive action limit of 0.0008 µg/L and an enforcement standard of 0.008 µg/L for PCBs in ground-water (3682).

WEST VIRGINIA
West Virginia currently has a water quality criterion of 1 ng/L for PCBs in Public A waters, but has proposed new criteria that are the same as the federal criteria. Final promulgation is expected in late spring 1989 (3835).

WISCONSIN
Wisconsin has set wild and domestic animal criteria for Arochlor in surface waters: Arochlor 1242 - 47 ng/L, Arochlor 1254 and 1260 - 3 ng/L, Arochlor 1016 - 233 ng/L (3842).

Proposed Regulations

- Federal Programs

Safe Drinking Water Act (SDWA)
EPA proposed a Maximum Contaminant Level (MCL) of 0.0005 mg/L, and a Maximum Contaminant Goal (MCLG) of zero for PCBs in drinking water in May, 1989, with final action scheduled for December, 1990 (3759).

Toxic Substances Control Act (TSCA)
EPA has proposed notification requirements for PCB waste handlers, manifest requirements to help track PCB waste disposal, and requirements that commercial storers of PCB waste obtain approvals from the EPA Regional Administrator, develop closure plans for their facilities, and demonstrate financial responsibility for their closure (3791).

- State Water Programs

MOST STATES
Most states are in the process of revising their water programs and proposing changes to their regulations which will follow EPA's changes when they become final. Contact with the state officers is advised. Changes are projected for 1989-90 (3683).

MINNESOTA
Minnesota has proposed a Recommended Action Level (RAL) of 0.05 µg/L for PCBs in drinking water (3451). Minnesota has also proposed chronic criteria of 0.05 µg/L for PCBs in ground-water and 0.00008 µg/L for surface water for the protection of human health (3452).

EEC Directives

Directive Relating to the Quality of Water for Human Consumption (540)

The maximum admissible concentration for PCBs is 0.1 μg/L. The total maximum allowable concentration for pesticides and related products is 0.5 μg/L.

Directive on the Quality Required of Shellfish Waters (537)

The mandatory specifications for organohologenated substances specify that the concentration of each substance in the shellfish water or in the shellfish flesh must not reach or exceed a level which has harmful effects on the shellfish and larvae. The specifications for organohalogenated substances state that the concentration of each substance in shellfish flesh must be limited that it contributes to the high quality of the shellfish product.

Directive on Ground-Water (538)

Direct discharge into ground-water (i.e., without percolation through the ground or subsoil) of organophosphorous compounds, organohalogen compounds and substances which may form such compounds in the aquatic environment, substances which possess carcinogenic, mutagenic or teratogenic properties in or via the aquatic environment and mineral oils and hydrocarbons is prohibited. Appropriate measures deemed necessary to prevent indirect discharge into ground-water (i.e., via percolation through ground or subsoil) of these substances shall be taken by member countries.

Directive on the Discharge of Dangerous Substances (535)

Organohalogens, organophosphates, petroleum hydrocarbons, carcinogens or substances which have a deleterious effect on the taste and/or odor of human food derived from aquatic environments cannot be discharged into inland surface waters, territorial waters or internal coastal waters without prior authorization from member countries which issue emission standards. A system of zero- emission applies to discharge of these substances into ground-water.

Directive on Marketing and Use of Dangerous Substances (541)
Polychlorinated biphenyls (except mono- and dichlorinated biphenyls) and preparations with a PCB content higher than 0.01% may not be used. Up to 30 June 1986 they were allowed for use under the following conditions:

- Closed system electrical equipment, transformers, resistors and inductors;
- Large condensers (>1 kg total weight);
- Small condensers, provided that the chlorine content of the PCBs is no greater than 43% and does not contain more than 3-5% of penta- and higher chlorinated biphenyls;
- Heat transmitting fluids in closed-circuit heat-transfer installations, except in those used for processing foodstuffs, pharmaceuticals and veterinary products;
- Hydraulic fluids utilized in underground mining equipment;
- Primary and intermediate products for further processing into other products not prohibited under the Directive.

Equipment, plant and fluids which were in service after 30 June 1986 shall continue to be authorized until they are disposed of or reach the end of their service life. Member states may prohibit this continued use for reasons of health and the environment.

Member states may also authorize the use of PCBs when it is not possible to use substitute products.

Directive on Toxic and Dangerous Wastes (542)
Any installation, establishment, or undertaking which produces, holds and/or disposes of certain toxic and dangerous wastes including phenols and phenol compounds; organic-halogen compounds; chrome compounds; lead compounds; cyanides; ethers and aromatic polycyclic compounds (with carcinogenic effects) shall keep a record of the quantity, nature, physical and chemical characteristics and origin of such waste, and of the methods and sites used for disposing of such waste.

Directive on the Classification, Packaging and Labeling of Dangerous Substances (787)
PCBs are classified as harmful substances and are subject to packaging and labeling regulations.

Directive on the Disposal of Polychlorinated Biphenyls and Polychlorinated Terphenyls (1239)
Member states must take measures to prohibit the uncontrolled discharge, dumping and tipping of PCBs or of objects containing PCBs. They must also take measures to make the disposal of PCB wastes compulsory and ensure that it is in a manner which does not endanger human health or the environment. Installations and establishments shall be authorized by member states for the purposes of disposing PCBs.

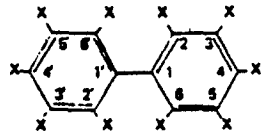
Directive on Transfrontier Shipment of Hazardous Waste (1433)
When the holder of a hazardous waste such as polychlorinated biphenyls intends to ship it to another member state, authorities of the member states concerned must be provided with information on the source and composition of the waste, measures to be taken to ensure safe transport, insurance against damage and the existence of a contractual agreement with the consignee of the waste. All transfrontier shipments must be properly packed and labeled and must be accompanied by instructions to be followed in the event of danger or accident.

EEC Directives - Proposed
Proposal for a Council Directive on the Dumping of Waste at Sea (1793)
EEC has proposed that the dumping of organohalogen compounds at sea be prohibited.Proposal for a Council Regulation Concerning Export From and Import Into the Community of Certain Dangerous Chemicals (1795[a]). EEC has proposed that any export of polychlorinated biphenyls on its own or in preparations must be reported by the exporter to a designated authority in the state of export and the state of import. The product must be packaged and labeled in accordance with the Directive on Classification, Packaging and Labeling of Dangerous Substances.

Resolution on a Revised List of Second-Category Pollutants (545)
Aroclor 1242 is one of the second-category pollutants to be studied by the Commission in the programme of action of the European Communities on Environment in order to reduce pollution and nuisances in the air and water. Risk to human health and the environment, limits of pollutant levels in the environment, and determination of quality standards to be applied will be assessed.

52.0 INTRODUCTION

This chapter encompasses a general review of the environmental fate, exposure and health effects of four commercial polychlorinated biphenyl (PCB) mixtures marketed in the U.S. under the name Aroclor® (Aroclor® 1016, 1242, 1254 and 1260). The Aroclor® formulations are complex mixtures of PCBs produced by progressive chlorination of biphenyl with anhydrous chlorine. The composition of the end product is determined by the degree of chlorination. The structural formula of PCBs and conventional numbering of substituent positions is shown in Figure 52-1.



x represents a chlorine or a hydrogen atom

FIGURE 52-1
STRUCTURAL FORMULATION OF PCBs

A total of 209 different biphenyls are theoretically possible by replacement of from one to ten hydrogen atoms on the biphenyl ring system by chlorine.

The individual Aroclor® mixtures are identified by four digits: the first two digits of most Aroclor® formulations, 12, indicate that the preparation is a mixture; the second two digits denote the approximate chlorine content by weight percent. For example, Aroclor® 1242 is a mixture with 42% average chlorine content. Aroclor® 1016 is a relatively recent mixture and does not conform to the above notation; its composition is similar to Aroclor® 1242.

The behavior of Aroclor® products in the environment is largely dictated by the behavior of the individual components of PCBs. The Environmental Fate and Exposure Pathways Section, therefore, focuses on data for the PCB components; where available, data specific to the four Aroclor® formulations are also included. The data provided in Section 52.3, Human Health Considerations, in contrast, are specific to the Aroclor® mixtures since the toxicology data are generally specific to each mixture.

52.1 MAJOR USES

Aroclor® compounds are very inert, thermally and chemically stable compounds with dielectric properties. They have been used in nominally closed systems as heat

transfer liquids, hydraulic fluids and lubricants, and in open-ended systems in which they came in direct contact with the environment as plasticizers, surface coatings, inks, adhesives, pesticide extenders and for microencapsulation of dyes for carbonless duplicating paper. In 1974, use of PCBs in the United States was limited to closed systems, i.e., approximately 70% of PCBs produced were used in capacitors while the remaining 30% were utilized in transformers (1457).

52.2 ENVIRONMENTAL FATE AND EXPOSURE PATHWAYS

52.2.1 Transport in Soil/Ground-water Systems

52.2.1.1 Overview

The environmental behavior of the Aroclor® mixtures is a direct function of their relative composition with respect to the individual chlorinated biphenyl species. Table 52-1 summarizes the approximate composition of the four Aroclor® products considered in this chapter. It is important to remember that Aroclor® formulations are mixtures and the physical properties and chemical behavior of mixtures cannot be precisely defined. The individual PCBs in a pure state are generally solids at room temperature; however, due to melting point depression, Aroclor® mixtures are oily to resinous liquids at ambient temperatures.

Individual PCBs vary widely in their physical and chemical properties according to the degree of chlorination and position of the chlorines on the biphenyl structure.

In general, as chlorine content increases, sorption increases while transport and transformation processes decrease. The specific PCB distribution measured in environmental samples may be distorted and may not correspond to the specific Aroclor® mixture responsible for the contamination. For this reason, most of the fate and transport discussion will focus on the chlorinated biphenyl species rather than the Aroclor® mixtures. In general, transport pathways can be assessed by using an equilibrium partitioning model, as shown in Table 52-2.

These calculations predict the partitioning of low soil concentrations of the PCB mixtures among soil particles, soil water and soil air; portions associated with the water and air phases of the soil have higher mobility than the sorbed portion. Estimates for the unsaturated topsoil model indicate that almost all (> 99.99%) of the Aroclor® formulations are expected to be associated with the stationary phase. Much less than 1% is expected to partition to the soil-water phase; therefore, only a small portion would be available to migrate by bulk transport (e.g., the downward movement of infiltrating water), dispersion and diffusion. An insignificant portion of the Aroclor® formulations is expected in the gaseous phase of the soil; diffusion of vapors through the soil-air pores up to the ground surface is not expected to be important. In saturated, deep soils (containing no soil air and negligible soil organic carbon), sorption is still expected to be the most significant fate process. Overall,

TABLE 52-1
APPROXIMATE COMPOSITION (%) OF AROCLOR® FORMULATIONS

	1016	1242	1254	1260
$C_{12}H_9Cl$	1	1	<0.1	ND[a]
$C_{12}H_8Cl_2$	20	16	0.5	ND
$C_{12}H_7Cl_3$	57	49	1	ND
$C_{12}H_6Cl_4$	21	25	21	1
$C_{12}H_5Cl_5$	1	8	48	12
$C_{12}H_4Cl_6$	<0.1	1	23	38
$C_{12}H_3Cl_7$	ND	<0.1	6	41
$C_{12}H_2Cl_8$	ND	ND	ND	8
$C_{12}H_1Cl_9$	ND	ND	ND	ND
Average M.W.	257.9	266.5	328.4	375.7

a) ND = nondetectable

Source: Callahan et al. 1979 (10)

TABLE 52-2
EQUILIBRIUM PARTITIONING CALCULATIONS FOR AROCLOR® 1016, 1242, 1254 AND 1260 IN MODEL ENVIRONMENTS[a]

Soil Environment	Estimated Percent of Total Mass of Chemical in Each Compartment		
	Soil	Soil-Water	Soil-Air
Unsaturated topsoil at 25°C[c]	>99.99	<0.01	<0.001
Saturated deep soil[d]	>99.75	<0.25	-

(a) Calculations based on Mackay's equilibrium partitioning model (34, 35, 36); see Introduction in Volume 1 for description of model and environmental conditions chosen to represent an unsaturated topsoil and saturated deep soil. Calculated percentages should be considered as rough estimates and used only for general guidance.

(b) Utilized range of estimated (611) soil sorption coefficients representing the biphenyls present at greater than 4% of the Aroclor® mixtures.

Aroclor® 1016: K_{oc} = 1E+05 to 2E+05
Aroclor® 1242: K_{oc} = 1E+05 to 6.3E+05
Aroclor® 1254: K_{oc} = 2E+05 to 5E+07
Aroclor® 1260: K_{oc} = 6.3E+05 to 1E+09

(c) Henry's law constant (atm · m^3/mol at 25°C) taken as: 3.2E-04 for Aroclor® 1016 (31), and 3.4E-04, 2.8E-04 and 3.4E-04 for Aroclor® 1242, 1254, and 1260, respectively (1571).

(d) Used sorption coefficient K_p = 0.001 K_{oc}.

ground water underlying PCB-contaminated soils is not expected to be vulnerable to contamination.

The persistence of PCBs in water systems is well documented; however, data on persistence in soil systems are much more limited. The distribution of PCBs in the soil/ground-water system following two separate accidental spills of Aroclor® 1254 have been documented (1580, 1588). In the first case, 6800 to 21,000 liters of transformer oil containing Aroclor® 1254 and chlorobenzenes were released after rupture of an underground pipe at a transformer manufacturing plant (1588). Large

quantities of PCBs were found to have migrated both vertically (nine meters through granular fill and fractured clay) and horizontally at the site; Aroclor® 1254 distribution was found to be very heterogeneous. The authors postulated that due to the low organic content (<1%) of soil at the site, PCB contamination existed in three phases: dissolved aqueous phase, sorbed phase and an oily liquid phase (Aroclor®/solvent mixture). Movement of the oily liquid was probably responsible for the downward migration of large quantities of PCBs through the clay fractures, as well as lateral movement through the fill. The isomer distribution pattern of PCBs at the surface was different from that of Aroclor® 1254, reflecting the preferential loss of the lower chlorinated biphenyls due to weathering and degradation.

A second spill of 1500 gallons of askarel (Aroclor® 1254/chlorinated benzene solution) also resulted in extensive vertical and horizontal soil contamination, as well as some ground-water contamination (1580). As in the other case, distribution in the soil/clay was non-uniform. Extensive rainfall following this particular spill also resulted in significant transport of Aroclor 1254 with surface runoff. Both of these spills involved large quantities of askarel (Aroclor® 1254 in chlorobenzene solvent), and the observed contamination patterns may result from saturation conditions in the topsoil and migration of a separate oily liquid phase.

52.2.1.2 Sorption on Soils

Adsorption to soils and sediments is the major fate process affecting PCBs in the environment. PCB adsorption has been studied and reviewed in a number of reports (10, 1583, 1589, 1590, 1534, 1591, 1592). In general, the rate of adsorption by soil materials was found to be rapid and conformed to the Freundlich adsorption equation (1583, 1596); adsorption capacity was highly correlated with organic content (1594, 596, 1592), surface area (1596) and clay content (1594, 1595) of the soil materials; PCBs were reported to be unable to penetrate into the inner surfaces of clay materials (1592). Desorption of sorbed PCB is not expected to be rapid (1593).

Distribution coefficients for PCBs on suspended solids in Saginaw Bay have been reported to range from 4×10^4 to 9×10^4 (1591). Representative partition coefficients for PCBs on actual soil materials are given in Table 52-3. In general, higher chlorinated isomers are more strongly sorbed; however, preferential adsorption is also dependent on ring position of the substituted chlorine (1592); values for K_{oc} range from approximately 10^3 for dichlorobiphenyl to 10^5 for octachlorobiphenyl (611).

Experimental studies (1583) on the mobility of Aroclor® 1242 and 1254 in soil materials indicate that these PCBs were sorbed strongly and remained immobile when leached with water or aqueous leachate from a waste disposal site. However, they were found to be highly mobile when leached with carbon tetrachloride. The mobilities of the PCBs were highly correlated with their solubilities in the leaching solvent and the organic content of the soil material. PCB mobility data, expressed as the ratio of the distance the PCBs moved to the distance the solvent traveled (R_f),

are presented in Table 52-4. It should be noted that even with carbon tetrachloride, a high percentage of the PCBs were retained on the soil while some moved with the solvent front.

Additional studies were performed by the same authors using different solvents and varying amounts of water; these data are presented in Table 52-5. Relatively small amounts of water (9%) in methanol were shown to significantly reduce the mobility of PCBs compared to the mobility in the pure solvent.

In summary, the available data indicate that sorption of PCBs, particularly the higher chlorinated biphenyls onto soil materials, will be rapid and strong. In the absence of organic solvents, leaching is not expected to be important, and PCBs are expected to be immobile in the soil/ground-water system; PCBs will be much more mobile in the presence of organic solvents. In the case of large spills of PCB/solvent mixtures, the soil and aqueous phases may become saturated resulting in a separate oily phase which may be more mobile.

TABLE 52-3
EQUILIBRIUM PARTITION COEFFICIENTS FOR PCBs

Aroclor®	Matrix	K	Organic Content (%)	Ref.
1254	Illite	1.4E+04	NA	1595
	Chlorite	1.0E+04	NA	
1242	Sand	22	<0.01	1592
	Montmorillonite Clay	172	0.9	
	Silt loam	532	4.3	

TABLE 52-4
MOBILITY OF AROCLOR® 1242 AND AROCLOR® 1254 IN SEVERAL SOIL MATERIALS WITH VARIOUS LEACHING SOLVENTS

		R_f Values					
	Organic Content	H_2O		Du Page Leachate		CCl_4	
	%	1242	1254	1242	1254	1242	1254
Ava silty clay loam	1.2	.02	.02	.02	.02	1.00	.96
Bloomfield loamy sand	0.2	.03	.03	-	-	-	-
Catlin silt loam	4.7	.02	.02	.04	.04	1.00	1.00
Catlin loam	0.6	.02	.02	.03	.03	1.00	1.00
Cisne silt loam	1.3	.03	.02	.03	.02	1.00	1.00
Coal char (1200F)	74	.03	.03	.04	.04	1.00	1.00
Drummer silt loam	2.2	.03	.03	-	-	1.00	1.00
Flanagan silt loam	2.6	.02	.02	.06	.05	1.00	1.00
Ottawa silica sand	<0.01	.03	.03	.03	.03	1.00	1.00

Source: Griffin and Chian (1583)

TABLE 52-5
MOBILITY OF AROCLOR® 1242 AND AROCLOR® 1254
ON SILICA-GEL TLC PLATES USING VARIOUS LEACHING SOLVENTS

	R_f VALUES	
	Aroclor®1242	Aroclor®1254
D.I. H_2O	0.15	0.15
DuPage leachate	0.15	0.15
80% H_2O and 20% Acetone	0.09	0.06
Acetone	1.00	1.00
15% H_2O and 85% Methanol	0.79	0.79
9% H_2O and 91% Methanol	0.80	0.83
Methanol	1.00	1.00
Benzene	0.99	0.95
Carbon tetrachloride	1.00	1.00

Source: Griffin and Chian 1980 (1583)

52.2.1.3 Volatilization from Soils

Transport of PCB vapors through the air-filled pores of unsaturated soils is not expected to be a rapid transport pathway. Modeling results indicate that a very small fraction of PCB loading will be present in the soil-air phase. On the other hand, volatilization (mostly from aqueous systems) and atmospheric transport are thought to account for the widespread, almost ubiquitous, distribution of PCBs in the environment. Several studies (1589, 1597, 1598, 1600) have shown that vapor phase transport can be a significant process for loss of PCBs from water bodies. Sorption to organic matter, however, has been shown to compete strongly with volatilization. Sorption onto suspended sediment has been presented as an explanation for the lower rates of volatilization exhibited for natural water bodies compared to estimated rates (10). Volatilization from soil was reported to be slow compared to volatilization from sand or PCB solution (1601).

Calculated half-lives for the volatilization of Aroclor® 1242, 1248, 1254 and 1260 from a 1 mm water column have been reported to range from 9.5 hours to 12.1 hours (1602); other authors have reported half-lives on the order of 3-4 hours for di- and tetrachlorobiphenyls (1597). Volatilization of Aroclor® 1260 from river water was reported to be only 67% after 12 weeks; after addition of sediment, the loss dropped to 34% after 12 weeks (1599, 1603). The Henry's law constants and volatilization half-lives do not vary widely with degree of chlorination of the PCBs.

The available data indicate that due to low water solubility, volatilization of water-borne PCBs not sorbed to sediment or suspended solids may be significant; when sorbed to soils/sediments, volatilization will be drastically reduced. However, since other fate and transport processes in the soil environment are relatively slow, volatilization of PCBs sorbed on surface soils may occur. Elevated airborne concentrations of PCBs have been measured near PCB disposal areas (1600).

52.2.2 Transformation Processes in Soil/Ground-water Systems

PCBs have been reported to be strongly resistant to chemical degradation by oxidation or hydrolysis. However, they have been shown to be susceptible to photolytic and biological degradation (10). Baxter and Sutherland (1572) have shown that successive biochemical and photochemical processes contribute to the degradation of PCBs in the environment. Experimental results indicate that the highly chlorinated PCBs can be photolytically degraded, resulting in the formation of lower chlorinated species and substituted products, as well as potential formation of biphenylenes and chlorinated dibenzofurans (1573, 1574, 1575, 1576); the presence of oxygen retards the photolytic degradation of PCBs.

There is some doubt as to the applicability of these photolysis experiments to environmental conditions, since they were generally carried out in organic solvents, often in the presence of other additives. However, since the rate of photolytic dechlorination is greatest for the highly chlorinated species (1576) (i.e., those species that are most resistant to biodegradation), photolytic degradation, although slow, may be a significant transformation process for these molecules. Furthermore, since they are rapidly sorbed to soils, these highly chlorinated PCBs may be concentrated in the surface layers and their actual photolysis rates may be higher than expected.

Microbial degradation has been reported to be an important transformation process for PCBs (10, 1577, 1578, 1579, 1581, 1582, 1583, 1584, 1585). In general, the lower chlorinated PCBs were more easily degraded than the higher chlorinated species. Position of chlorine substitution on the biphenyl molecule also affected the rate of PCB degradation. Biodegradability of PCBs has been reported to be a function of the number of carbon-hydrogen bonds available for hydroxylation by microbial oxidation; adjacent unchlorinated carbons have been shown to facilitate metabolism through formation of arene oxide intermediates (10). Both aerobic oxidative biodegradation and anaerobic dechlorination have been identified as PCB transformation processes in Hudson River sediments (1585). Composting studies

(1582) indicate that aerobic systems exhibited greater PCB reductions than anaerobic systems (42 to 48% vs. 18 to 28% reduction, respectively, after two weeks).

The biodegradation of Aroclor® 1016, 1242, 1254 and 1260 is a function of the relative content of the lower chlorinated biphenyls. Aroclor® 1016 and 1242 are largely comprised of di-, tri-, and tetra- chlorobiphenyls, which have been shown to be biodegraded in microbial cultures, aquatic systems and soils at fairly rapid rates (1583, 10, 1584, 1582, 1577, 1579). Aroclor® 1254 and 1260 are largely comprised of higher chlorinated species and are expected to be resistant to biodegradation. In fact, Liu (1579) reported that an increase of chlorination from monochlorobiphenyls to predominantly trichlorobiphenyls (Aroclor® 1016 and 1242) and pentachlorobiphenyls (Aroclor® 1254) resulted in a corresponding decrease in degradation from 100% to 29% and 19%, respectively; similar results were reported by other authors (1586). In an experiment with reservoir sediment, Aroclor® 1254 was degraded approximately 50% in six weeks (846). Using an acclimated semi-continuous activated sludge experiment with 48-hour exposure, degradation rates of 33%, 26% and 19% were determined for Aroclor® 1016, 1242 and 1254, respectively (1586).

A study of the fate of Aroclor® 1254 in soil and ground water after an accidental spill showed essentially no reduction in Aroclor® 1254 concentration due to biodegradation after two years (1580). On the other hand, other authors (1584) reported moderate biodegradation of Aroclor® 1254 in soils (40% degraded in 112 days) and no degradation of Aroclor® 1260 (primarily hexa- and hepta-chlorobiphenyls). The presence of the lower chlorinated biphenyls has been shown to actually increase the rate of biodegradation of the higher PCBs through co-metabolism (1581, 1579, 1583, 1587).

In summary, most studies have reported substantial PCB degradation in aqueous solutions; biodegradation rates are greatest for the lower chlorinated species. While adsorption of PCBs by soil and competition by native soil organisms may alter the degradation rate, several authors have reported substantial PCB degradation in soil systems (1582, 1583, 1584). Mixed cultures of PCB-degrading microbes have been isolated from PCB-contaminated soils (1583), suggesting that PCBs will be degraded to some extent in the environment.

52.2.3 Primary Routes of Exposure from Soil/Ground-water Systems

The above discussion of fate pathways suggests that PCBs in general have a low volatility, are very strongly sorbed to soil, and have a high potential for bioaccumulation. These fate characteristics suggest several potential exposure pathways.

Volatilization of PCBs from a disposal site is not likely to represent an important exposure pathway under most conditions. Tofflemire and Shen (1808) concluded, however, that volatilization of PCBs was of greater concern than ground-water contamination for a number of open PCB dump sites and dredge spoil sites along the

upper Hudson River. Some control programs had been initiated to prevent ground-water contamination.

Drinking water contamination resulting from the migration of PCBs into ground water may occur, although PCBs are relatively immobile in soil. Mitre (83) reported that PCBs have been found at 58 of the 546 National Priority List (NPL) sites. They were detected in 32 sites in ground water, 48 sites in surface water and 4 sites in air. In the National Organics Monitoring Survey conducted in 1976-77, PCBs were found in 6% of the finished ground-water supplies at levels of 0.1 μg/L (992). One state also reported that PCBs were detected in 32 of the 163 ground-water supplies sampled, with concentrations as high as 1.27 μg/L (992). These data do indicate that ground-water contamination by PCBs can occur in some situations.

The movement of PCBs in ground water or, more likely, their movement with soil particles may result in discharges to surface waters. As a result, ingestion exposure may occur through the use of surface waters as drinking water supplies, and dermal exposures may result from the recreational use of surface waters. More importantly, however, is the potential for uptake of PCBs by aquatic organisms or domestic animals. The high bioconcentration factor and the persistence of PCBs suggest that these can be important exposure pathways. In fact, such contamination has been documented in a number of cases (1801).

52.2.4 Other Sources of Human Exposure

As a result of their widespread use over a number of years, PCBs are now considered ubiquitous pollutants. Results from the National Human Adipose Tissue Survey (NHATS) show that in 1981 greater than 99% of the U.S. population had measurable levels of PCBs in fatty tissues (1807).

Exposure sources for PCBs are numerous. As mentioned above, PCBs were found to some extent in ground-water drinking water supplies. They were also found in 2% of finished surface water systems at concentrations less than or equal to 1.4 μg/L (992).

PCBs are also commonly found in air, resulting in low level inhalation exposures at most locations. Eisenreich et al. (1810) reported ranges of concentrations for remote areas of 0.02-0.5 ng/m^3, 0.1-2 ng/m^3 for rural areas, and 0.5-30 ng/m^3 for urban areas. For the most part, the measurements most closely represent Aroclor® 1242, 1248 and 1254 (1806).

As for many other persistent organic compounds, PCBs in food can represent a significant source of exposure. Gartrell et al. (1244) reported average dietary intakes of PCBs ranging from nondetectable (ND) to 0.099 μg/kg of body weight/day for infants and toddlers during the years 1976-1979. Adult intakes ranged from <0.0001 to 0.027 μg/kg/day over the same time period (1245). The largest sources of exposure are meat, fish and poultry. Other specialized studies of the components of

the diet have taken place. For example, Frank et al. (1247) reported 0.033 ppm PCBs in bovine milk fat and various authors have reported PCBs in mother's milk (1805, 1802, 1803). In addition, fish contamination problems have occurred in a number of locations. The National Fish Monitoring Program collected fish from 107 stations in major rivers around the U.S. and in the Great Lakes. A total of 315 composite samples were collected. PCBs were reported at 94% of the stations sampled; the wet-weight mean residue concentration reported was 0.53 μg/g total PCBs. Residues similar to Aroclor® 1260 were most prevalent, and Aroclor® 1254 and 1248 were less prevalent (1800).

Direct exposure to PCBs has occurred in the past. For example, Schecter (1804) reported the contamination of an office building by PCBs resulting from overheating of an electrical transformer.

52.3 HUMAN HEALTH CONSIDERATIONS

52.3.1 Animal Studies

52.3.1.1 Carcinogenicity

Among the PCB mixtures tested in chronic oral exposure studies with laboratory animals, Aroclor® 1254 and Aroclor® 1260 were found to induce liver neoplasms. There are no data available for Aroclor® 1016 or Aroclor® 1242.

IARC has determined that although there is limited evidence to confirm PCBs as human carcinogens, there is sufficient evidence of the carcinogenic effect of PCBs in animals. Based on the IARC rating system, PCBs were classified as Group 2A compounds (3315). The USEPA (3948) considers the PCBs to be a Class 2B carcinogen.

Aroclor® 1016 and Aroclor® 1242

No data on carcinogenicity are available.

Aroclor® 1254

Kimbrough and Linder (1240) fed 300 ppm Aroclor® 1254 to male BALB/cJ mice for 11 months or for 6 months followed by the control diet for the remaining 5 months of the study. In the mice fed Aroclor® 1254 for 11 months, hepatomas were observed in 9/22 (41%) survivors and adenofibrosis and enlarged livers in all 22 survivors. Examination of livers of mice treated for 6 months and then allowed to recover for 5 months showed slight-to-moderate diffuse, interstitial fibrosis. One mouse developed a small hepatoma. No hepatic lesions were observed in 58 control mice.

In a study conducted by the National Cancer Institute (NCI) (1283, 1193), male and female F344 rats were administered 0, 25, 50 or 100 ppm Aroclor® 1254 daily for 104-105 weeks. Clinical signs of toxicity including alopecia, amber-colored urine, facial edema, exophthalmos and cyanosis were observed in the 50 or 100 ppm Aroclor® 1254 groups. An increased incidence of lymphoma and leukemia combined was seen in males (12.5% for control animals, 8.3% for the low dose animals, 20.8% for the 50 ppm group and 37.5% for the high dose group). However, comparisons of each treatment group with the matched controls were not statistically significant and the tumors could not clearly be related to Aroclor® 1254 treatment. Hepatocellular adenomas and carcinomas were found in Aroclor® 1254-treated animals but not in control animals. Furthermore, a dose-related incidence of nodular hyperplasia appeared in all animals treated with Aroclor® 1254 but this trend was not statistically significant. Adenocarcinomas of the stomach, jejunum or cecum were observed in 2 treated male and 2 treated female rats as well as a carcinoma in a treated male. These lesions, although not statistically significant, appear to be treatment-related since no control animals developed these types of tumors. NCI concluded that Aroclor® 1254 was not carcinogenic in F344 rats but that the high incidence of hepatocellular proliferative lesions in both male and female rats was Aroclor® 1254-related. Also, the tumors found in the gastrointestinal tract may also have been due to Aroclor® 1254 administration.

Morgan et al. (1194) limited their investigation to the gastric effects of PCBs. Male and female F344 rats were fed a diet containing 0, 25, 50 or 100 ppm Aroclor® 1254 for 26 months. Rats fed 50 or 100 ppm Aroclor® 1254 had a lower body weight than the control animals and developed signs of PCB toxicity. The incidence of stomach lesions increased as the dietary intake of Aroclor® 1254 increased. In control animals, 6.4% developed lesions while in the 25, 50 and 100 ppm PCB-treated groups, 10.4%, 16.7% and 35.4% developed lesions, respectively. A total of 6 definite and 2 suspected, but not confirmed, adenocarcinomas developed in Aroclor® 1254-fed rats. Adenocarcinomas rarely occur in F344 rats. Morgan et al. concluded that Aroclor® 1254 incorporated into the diet for 2 years induced intestinal metaplasia which resulted in the probable induction of adenocarcinomas in F344 rats.

Hendricks et al. (3286) fed rainbow trout for a year on Aroclor® 1254, Aflatoxin B1 or Aroclor® plus Aflatoxin. No liver tumors were observed in the trout fed Aroclor® alone, and the fish fed Aroclor® 1254 plus Aflatoxin B1 had less liver tumors than fish fed Aflatoxin B1 alone.

Aroclor® 1260

Norback and Weltman (1169, 1170) fed Sprague-Dawley rats Aroclor® 1260 in the diet at a level of 100 ppm for 16 months, followed by 50 ppm for 8 months and finally, a control diet for 5 months. Hepatocellular tumors developed in 95% of the female rats and 15% of the male rats. Seventy percent of the females also developed various forms of bile duct tumors; only 37% of the males developed such tumors.

Norback and Weltman concluded that Aroclor® 1260 was a complete liver carcinogen acting as both an initiator and promotor.

Kimbrough et al. (1171) studied the effect of this Aroclor® congener in female Sherman rats fed 0 or 100 ppm Aroclor® 1260 for 21-22 months. Hepatocellular carcinomas developed in 14.13% of the treated rats and in only 0.58% of control animals. Treated rats also developed a high incidence of neoplastic liver nodules (79.5% vs. zero in control animals) and hepatocellular alterations (98.9% vs. 16.2% in control rats).

Groups of male Wistar rats were fed a protein diet containing 50 ppm or 100 ppm Aroclor® 1260 for 120 days (3580). Gross hepatic changes, neoplastic nodules and adenofibrosis in 75% and 50% of the treated animals, respectively, were observed. The authors were unable to explain the higher incidence of tumors found in the rats fed the lower concentration of Aroclor.

Male Wistar rats were fed a standard diet, a diet supplemented with 100 ppm Clophen A30 or a diet supplemented with 100 ppm Clophen A60 for 832 days (3617). Clophen A60 is almost identical in composition to Aroclor® 1260 (3031), while Clophen A30 appears to be similar in structure to Aroclor® 1016. After 800 days, none of the control animals, 2% of the Clophen A30 animals and 21% of the Clophen A60 animals sacrificed had liver carcinomas (0, 1 or 7%, respectively, of the total animals). Hepatocellular carcinoma was the most frequently found lesion in animals sacrificed at the end of the experiment, observed in 2, 3, and 61% of the animals in the control, Clophen A30 and Clophen A60 groups, respectively. Preneoplastic nodules and neoplastic lesions were found in 50-60% of the Clophen A30 animals after day 500, and 100% of the animals killed after day 800. However, 100% of the Clophen A60 animals had preneoplastic and neoplastic lesions after day 500. The incidence of preneoplastic nodules and neoplastic lesions in control animals was low until day 800 after which the incidence rose to 32%.

52.3.1.2 Genotoxicity

The polychlorinated biphenyls, specifically the Aroclors, have proved to be an enigma with respect to genotoxic effects in the systems in which they have been tested.

Schoeny et al. (3626) tested Aroclor® 1254 at eight concentrations over a 3-log dose range in four strains of Salmonella (TA98, TA100, TA1535 and TA1537) with and without metabolic activation and found it to be nonmutagenic. Aroclor® 1254 at concentrations up to 10,000 μg/plate was also tested for the National Toxicology Program in the above strains as well as in TA97, with and without Aroclor® 1254-induced rat or hamster liver S9 (10% and 30% liver S9 from each of the induced animal sources); it was negative in all five strains under all test conditions (3860). In a collaborative study involving 4 laboratories, Aroclor® 1254 was tested blind for histidine revertants in the five standard strains of Salmonella and for tryptophan

revertants in Escherichia coli WP2(uvrA) in concentrations ranging from 0.3 to 333.3 µg/plate and was also found to be negative (3188).

Shelton et al. (3639) also found 500 µg/plate to be nonmutagenic in strain TA98 using trout liver S20 for an activation system. Wyndham et al. (3851) observed a dose-dependent increase in revertants of Salmonella typhimurium TA1538 treated with Aroclor® 1221 but not with Aroclor® 1268 in the presence of rabbit liver microsomes, results that lead the authors to speculate that "as the degree of chlorination decreased the mutagenicity increased."

Sina et al. (3657), using alkaline elution as a means of observing DNA damage, observed that treatment with 0.3, 1.0 and 3.0 mM Aroclor® 1254 induced DNA breaks in freshly perfused rat hepatocytes treated for 3 hrs.

Hoopingarner et al. (3297) treated human lymphocytes with 100 ppm Aroclor® 1254 for one cell cycle, and observed no chromatid breaks above control levels.

Garrett and Lewtas (3236) observed that Aroclor® 1248 and Aroclor® 1254 significantly inhibited DNA synthesis and protein synthesis in CHO cells.

No mutagenic activity was evident for Aroclor® 1242 in a mammalian cell assay using V79 Chinese hamster cells (1180).

Male house fly larvae fed Aroclor® 1254 and examined as adults were observed by Yousef et al. (3858) to have abnormal and degenerating spermatids which they attributed to tubulin effects.

In a study on the effects of sublethal doses of Aroclor® 1254 on Atlantic codfish, Freeman et al. (3227) observed spermatogenic arrest in the testes of males fed Aroclor® 1254.

Sperm count but not sperm motility was significantly reduced in the American kestrel, Falco sparverius, when 9 to 10 mg/kg Aroclor® 1254 was injected intramuscularly into cockerels (3067).

Sirianni and Huang (3659) injected mice intraperitoneally with Aroclor® 1254 then implanted diffusion chambers containing Chinese hamster V79 cells into the peritoneal cavity of the treated mice. They subsequently examined the V79 cells for sister chromatid exchanges which proved to be at control levels.

Dikshith et al. (3173) gavaged male Sprague-Dawley rats with 50 mg/kg Aroclor® 1254 for seven consecutive days and examined testicular metaphases at intervals after treatment; they found no evidence to suggest that this PCB causes significant chromosome damage.

Robbiano and Pino (3598) demonstrated that Aroclor® 1254 administered to male Sprague-Dawley rats either by gavage or intraperitoneally significantly increased DNA single strand breaks in liver cells.

Sager (3607) reported that rat males treated as pups through Aroclor® 1254-gavaged lactating dams and mated at age 130 days to untreated females showed a significant reduction in reproductive performance and in the numbers of implants and live fetuses observed.

In a cytogenetic study, Garthoff et al. (3237) observed no significant increase in chromosomal aberrations above controls in Holtzman male rats fed 500 ppm Aroclor® 1254 in their chow for 34 to 37 days; spermatogonia as well as bone marrow cells were examined.

Topham (3724) injected male CBCF$_1$ mice daily for 5 days with Aroclor® 1254 in concentrations ranging from 500 to 1000 mg/kg, examined caudal sperm for morphological abnormalities five weeks after the last treatment and observed no effect significantly different from controls.

Green et al. (1181) studied the effects of Aroclor® 1242 on bone marrow cells and spermatogonia in Osborne-Mendel rats. A single oral dose of 1250, 2500 or 5000 mg/kg or a multiple dose of 500 mg/kg/day Aroclor® 1242 for 4 days was administered. Neither reduction of mitotic index or increase in chromosomal abnormalities was observed in both tissues. Aroclor® 1254 was also given orally in doses of 75, 150 or 300 mg/kg/day for five days with no significant increase in chromosomal abnormalities in bone marrow cells.

Green et al. (1182) also tested Aroclors 1242 and 1254 in the dominant lethal assay using Osborne-Mendel rats. Male rats were gavaged with a single dose of 625, 1250 or 2500 mg/kg or multiple doses of 125 or 250 mg/kg/day Aroclor® 1242 for 5 days, then bred to untreated females. No significant effects were observed on embryo implantation or lethality in any of the treatment groups. When male rats were gavaged with 75 or 150 mg/kg/day for 5 days of Aroclor® 1254, no significant dominant lethal effects were observed.

52.3.1.3 Teratogenicity, Embryotoxicity and Reproductive Effects

Numerous publications have demonstrated the ability of PCBs to cross the placenta and accumulate in fetal tissues. However, indications of structural malformations, genetic changes or other teratogenic effects have been few; most oral exposure studies have been negative. Reproductive capacity can be notably depressed with PCB exposure, particularly in females.

Aroclor® 1016

Adult female rhesus monkeys were fed diets containing 0, 0.25 or 1 ppm Aroclor® 1016 daily throughout gestation and throughout a 4-month nursing period (total exposure of 21-22 months) (1186). There was no significant difference in the number of breeding attempts between the control and treated groups and all monkeys delivered viable offspring. Birth weights of the offspring born to the 1 ppm treated monkeys were significantly lower than the controls (422 g vs. 512 g for controls) but no other significant differences were noted between treated and control offspring. The PCB content in the skin of offspring at birth was 1.54 ppm for controls, 1.65 ppm for the 0.25 ppm treated group and 3.37 ppm for the 1 ppm treated group. After nursing for 4 months, mesenteric fat tissue of offspring of treated mothers contained 10.3 and 27.5 ppm Aroclor® 1016 in the 0.25 and 1 ppm treated animals, respectively. Eight months post-weaning, mesenteric fat PCB levels had dropped to 1.96 and 3.75 ppm, respectively. This study indicates that Aroclor® 1016, even when administered at doses low enough not to cause toxicity in the adult, accumulates in the adipose tissue and subsequently is transferred to the offspring via the placenta and the milk.

Taylor et al. (3703) examined personnel records from PCB manufacturing facilities engaged in producing capacitors using Aroclor® 1016, Aroclor® 1254 and Aroclor® 1242. There was a total of 388 pregnancies to 354 females and 51 births to 39 females who worked directly with PCB manufacturing. High exposure to PCBs was associated with reduced birth weight even after adjustment for year of birth, maternal parity, and sex of infant. Mean gestation age was reduced by 6.6 days after adjustment for these same variables. After adjusting for gestational age, the average birth weight in the high exposure group was reduced by 58 grams.

No deleterious effects on reproduction resulted in rats fed 1 or 10 ppm Aroclor® 1242. However, rats fed 100 ppm had reduced mating indices in second generation animals (1460). In addition, Keplinger (1461) also observed a reduced survival rate in offspring of rats fed 100 ppm Aroclor® 1242.

Gellert and Wilson (3239) observed no reproductive effect when female rats were gavaged daily on days 14-20 with 30 mg/kg Aroclor® 1242. Body and organ weights of the male and female offsprings were similar to those of the controls at 6 months of age. The fertility of the male offsprings was unaffected and they produced an F_2 generation which had a normal sex ratio.

No teratogenic effect was reported in a swine reproduction study conducted by Hansen et al. (3266). However, the 3rd litter sows, fed at dose levels of 20 ppm of Aroclor® 1242 for one estrous cycle before mating and throughout gestation, did farrow a significantly decreased number of live pigs. Treated sows also had more mummified fetuses.

As discussed above, Taylor et al. (3703) reported shortened gestation periods and reduced birth weights in pregnant women occupationally exposed to Aroclor® 1242.

Aroclor® 1254

Severe reproductive failure occurred in female minks following oral administration of 1, 5 or 10 ppm of Aroclor® 1254 for 4 months. The rates of conception were 8/10, 3/12 and 0/6, respectively, compared to 11/11 in controls. Decreased fetal survival was also evident; the incidences of live births were 3/9 (33%), 33/43 (77%) and 56/66 (85%) for the 5 ppm, 1 ppm and control groups, respectively (1191, 1187).

Aulerich et al. (3042) observed similar reproductive failure in female minks fed 2.5 ppm of Aroclor® 1254 for one month prior to mating and through parturition. Only one of ten treated females whelped a kit and it was stillborn.

Truelove (1160) investigated the teratogenic and embryotoxic effects of ingested Aroclor® 1254 on cynomolgus monkeys. Beginning on day 60 of gestation, two pregnant monkeys were given 100 μg/kg/day, one monkey was given 400 μg/kg/day and one monkey served as a control. Treatments were administered daily throughout gestation and post-partum. Offspring of both monkeys fed 100 μg/kg Aroclor® 1254 were delivered stillborn. The 400 μg/kg treated monkey delivered a live offspring, but both the birth weight and the weight gain for the next 130 days was significantly reduced. The offspring died on day 139 due to impaired immunological function. Autopsy revealed acute bronchopneumonia. The only maternal clinical sign of toxicity was the loss of fingernails in one of the 100 μg/kg treated monkeys and the 400 μg/kg treated monkey. All treated adult monkeys also showed signs of diminished immunologic capacity on day 50 post-partum (148 days of treatment). At autopsy, the PCB concentrations of the liver and kidney in the 400 μg/kg treated dam were 7.17 ppm and 1.88 ppm, respectively. The nursing infant of this dam had a liver PCB concentration of 47.94 ppm and a kidney concentration of 23.72 ppm. PCB content in the adipose tissue of the exposed infant increased from 35 ppm at 5 days of age to 483 ppm on day 139 when the infant died. These high accumulations of PCBs in the infant resulted from the transfer of PCBs from the mother to the infant via the milk.

Spencer (1196) fed female albino rats 0, 25, 50, 100, 200, 300, 600 or 900 ppm Aroclor® 1254 daily on days 6 through 15 of gestation. No embryonic resorption was observed by day 12 in females fed up to 900 ppm Aroclor® 1254. Maternal toxicity was seen at 600 and 900 ppm levels. Fetotoxic effects were present in the form of decreased fetal survival rates at levels of 300 ppm and above and reduced birth weight at 100 ppm or more.

Male and female Wistar rats were given drinking water containing 70 ppm Aroclor® 1254 for 9 weeks. After the first week of treatment, treated rats were allowed to mate with control rats. No adverse effects on the fertility of male rats

exposed to Aroclor® 1254 were noted. Several treated females died during the 7th week and by the 9th week, fetal resorption was obvious. By the end of the 9th week, both the treated males and females were returned to ordinary tap water. Biochemical studies revealed that Aroclor® 1254 elevated the mixed function oxidase activity. This increase persisted even after exposure to Aroclor® 1254 was terminated and rats were given tap water (1197).

Overman et al. (3544) exposed female rats from mating to weaning of pups to 2.5, 26, or 269 ppm of Aroclor® 1254 in their diet. The high dose decreased the number of litters and lowered average pup birth weight. Most of the pups in this group died during the first 8 days after birth. The only toxic effects observed in the 2.5 or 26 ppm groups were reduced pup growth and delays in some neurobehavioral assessments. These delays occurred in a dose-related manner. No physical deformities, reduction in litter size, increase in dead pups, or change in sex ratio was observed in any treatment group.

PCBs have the ability to induce the liver mixed function oxidase system which results in a faster than normal rate of metabolism of endogenous substrates such as steroid hormones. The decrease in steroid hormones is expected to affect reproduction. To investigate this effect, Brezner et al. (1162) orally administered 0 or 10 mg/kg Aroclor® 1254 daily for at least 30 days to female Wistar rats that had just delivered litters. The only PCB exposure to the pups was via the mother's milk. Over the 4 week dosing period, maternal rats experienced a significant weight loss. Rats exposed for 6 weeks exhibited a significantly prolonged estrous cycle (67.3% of the treated rats were affected vs. 6% in control rats). Receptivity of females was decreased in the treated rats, i.e., sperm were present in the vaginal smears of only 79.5% of the treated females vs. 100% in the control females. Among pregnant females, 89% of the treated females completed pregnancy vs. 100% of control females. Vaginal bleeding occurred in 71% of treated females on days 10-15 of gestation and 71% of the treated females delivered 1-3 days late while only 21% of controls showed vaginal bleeding and 10% delivered late. The average litter size of PCB-treated rats was smaller than normal (6.5 vs. 10 pups in the control group) and an average of 1.5 pups/litter were dead in the treated group. Development of the pups from treated dams was slower and an increase in mortality was seen before weaning. In female offspring of the Aroclor® 1254-treated group, vaginal opening occurred at an earlier age (39 days vs. 43 days in control animals) and there was a significant delay in the appearance of first estrus (8 days vs. 4.4 days in the control animals). Other reproductive parameters were not affected. Once PCB exposure ceased, body weight reached control values within 2-3 months and a reversal of the adverse reproductive effects was seen.

Sager and Girard (1161) expanded the findings of Brezner et al. (1162) and reported the results of early postnatal exposure of rats to Aroclor® 1254 on reproductive performance later in life. Mothers of the test group were fed 0, 8, 32 or 65 mg/kg Aroclor® 1254 on days 1, 3, 5, 7 and 9 of lactation. Offspring were then allowed to mature to either young or mature adults. Vaginal opening and first

estrus were delayed in offspring exposed to PCBs. In the mature adult group, the incidence of pseudopregnancy in animals exposed to 32 mg/kg early in life was markedly increased. In the high dose group, implantation was significantly inhibited. Also, mature adults in the 32 or 65 mg/kg exposure groups exhibited increased embryonic deaths. Sager and Girard concluded that rats exposed to PCBs early in life through mother's milk experienced reproductive dysfunction in adult life despite decreasing PCB levels in the body tissue.

Sager (1163) studied the early postnatal effect of PCBs on adult male reproduction in Holtzman rats. Lactating dams were orally administered 0, 8, 32 or 64 mg/kg Aroclor® 1254 on days 1, 2, 3, 5, 7 and 9. Males were weaned on day 23, allowed to mate beginning on day 130 and autopsied on day 165. Any pregnant females resulting from the mating period were autopsied on day 11-12 of gestation. Examination of the pregnant females revealed a decreased number of implantations and significantly fewer surviving fetuses. The resorption rate was significantly increased and significantly fewer females became pregnant after exposure to the treated males. Treated males showed a reluctance to mate. Prostate weight was significantly lower in treated male offspring. Seminal vesicle weight was also decreased in males exposed to the top 2 dosages while testes weight was significantly increased.

In a multi-generation study in white-footed mice, Linzey (3399) observed that diets containing 10 ppm Aroclor® 1254 resulted in reduced weight in the offsprings (F_1 and F_2) and poor reproductive success in the second (F_1) generation.

As discussed above in the section on Aroclor® 1016, Taylor et al. (3703) reported shortened gestation periods and reduced birth weights in pregnant women occupationally exposed to Aroclor® 1254.

Aroclor® 1260

Aroclor® 1260 was fed to rats at a concentration of 0, 1, 10 or 100 ppm. No effect was seen at the 1 or 10 ppm treatment level. Ingestion of 100 ppm Aroclor® 1260 resulted in an increased incidence of stillbirths (1460).

Calandra (3095) fed rats a diet containing 1, 10, or 100 ppm Aroclor® 1260 during a three generation reproduction study. No reproductive or teratogenic effect was observed in the first generation; however, a decrease in the mating index and in the incidence of pregnancy was observed in the 10 and 100 ppm groups in the second and third generations.

52.3.1.4 Other Toxicologic Effects

A number of issues arise with regard to an assessment of the toxicity of various Aroclor® congeners. Studies have shown that the degree of toxicity depends on both the number and location of the halogen atoms. In addition, the relationship between

dose and time must be considered since a lower dose may be able to produce a given level of intoxication if exposure is extended, due to the accumulative nature of these compounds. Finally, the type of toxic reaction or the dose required to elicit a reaction may vary considerably with different species. In general, non-human primates are more susceptible to PCB intoxication than rabbits and rats; females are generally more susceptible than males, and the young are generally more susceptible than adults.

52.3.1.4.1 Short-term Toxicity

In most species, the first sign of acute intoxication with PCBs is usually weight loss or reduced weight gain. Severely intoxicated rats have exhibited ataxia, diarrhea and lack of response to pain stimuli; histopathological changes are observed primarily in the liver and kidney. The median time to death is usually 2-3 weeks for small laboratory animals.

An oral LD_{50} of 2300 mg/kg (3933) has been reported in the rat for Aroclor® 1016. Oral LD_{50} values in adult rats range from 794 to 1269 mg/kg (355), 1295 to 2000 mg/kg (355) and 4000 to 10,000 mg/kg (59) for Aroclor® 1242, 1254 and 1260, respectively. An oral LD_{50} of 1315 mg/kg Aroclor® 1260 has been reported for weanling rats (3031). Toxicity generally decreases with increased chlorination (1178).

Aroclor® 1016

Alvares et al. (1275) intraperitoneally administered 50 mg/kg Aroclor® 1016 to male Sprague-Dawley rats for 4 days. Rat livers were examined 24 hours after the last treatment. Aroclor® 1016 was shown to induce a significant increase in liver microsome protein. The cytochrome P-450 content was doubled and the ethylmorphine N-demethylase activity was shown to triple while benzo(a)pyrene hydroxylase induction increased only 50% over control levels. In contrast, Ueng and Alvarez (3752) reported inhibitory effects on the P-450-dependent monooxygenases in liver and lung of rabbits treated with 100 mg/kg/day Aroclor® 1016 for 4 days.

Aroclor® 1242

Bruckner et al. (1279) orally administered 2.5, 4 or 6 g/kg Aroclor® 1242 to male Sprague-Dawley rats. After 4 hours of dosing, animals in all treatment groups exhibited loose stools, diminished exploratory behavior and decreased response to pain stimuli. Animals also developed an unusual stance characterized by an arching of the back and an elevated posterior portion of the trunk. Within the next 24 hours, rats treated with 6 g/kg Aroclor® 1242 developed profuse diarrhea, adipsia (avoidance of drinking), oliguria, anorexia, erythema of the limbs and weakness. Ataxia, coma and death followed. Progressive dehydration was evident as shown by a decreasing body weight and increasing packed cell volume. Animals in the 2.5 g/kg treatment group gradually improved and only showed slight signs of oliguria and anorexia 72 hours after dosing. Blood analysis of rats given 4 g/kg Aroclor® 1242

showed a greater proportion of polymorphonuclear leukocytes than in control rats. Also, many erythrocytes were crenated (scalloped or notched). Necropsy revealed minute, pale foci in the liver. Microscopic examination showed fatty deposits and necrotic foci of vacuolated hepatocytes. Widely scattered areas of vacuolated tubular epithelial cells similar to those observed in the hepatocytes were found in the kidney. All other tissues were normal.

Aroclor® 1254

Carter (1164) investigated the effect of Aroclor® 1254 on liver weight in male Fischer rats fed 0 or 20 ppm Aroclor® 1254 in the diet for either 1, 2, 4, 8 or 14 days. There was no significant difference in cumulative food consumption between the control group and the 20 ppm group regardless of the duration of treatment and body weights were comparable. However, a significant increase in liver weight was noted on day 4 of treatment which continued throughout the experiment. This increase in liver weight was due to the toxic effect of Aroclor® 1254 on centrilobular hepatocytes which resulted in hypertrophy of the cells.

Carter and Mercer (1198) examined the toxic effect of Aroclor® 1254 as distinguished from the effects of decreased food consumption associated with high PCB exposure. Male Fischer rats were fed 0, 150 or 350 ppm Aroclor® 1254 for 10 days. Based on the quantity of food consumed in each treatment group, additional groups of rats were fed the same amount of food minus Aroclor® 1254. No significant change in kidney weight was observed. Spleen weight was significantly decreased in both the 350 ppm- treated rats and in the pair-fed controls, indicating that the depression in food consumption was responsible for the decreased spleen weight and not the PCB. Aroclor® 1254 did have an effect on liver weight. Animals in the 150 or 350 ppm group both showed a statistically significant increase in liver weight over both the control and pair-fed animals.

Carter (1165) also investigated whether low levels of Aroclor® 1254 administered over relatively short periods of time would induce the hypercholesterolemia usually observed after long term exposure to high levels of PCBs. Male Fischer rats were fed diets containing 0, 2, 4, 8, 16 or 32 ppm Aroclor® 1254 for 4 days. No effect on body weight gain, final body weight or the total food consumption was observed. Liver weights were significantly increased in the animals fed 16 or 32 ppm Aroclor® 1254 for the 4-day test period and serum cholesterol levels were significantly elevated in the 8, 16, 32 ppm treated animals. Serum high density lipoprotein cholesterol levels were elevated in all PCB-treated groups but significantly elevated only in the 32 ppm-treated group.

Aroclor® 1260

No compound-specific data were found on acute toxic effects of Aroclor® 1260.

52.3.1.4.2 Chronic Toxicity

Aroclor® 1016

The effect of chronic exposure to Aroclor® 1016 on immunological function was studied by Silkworth and Loose (1188). C57BL/6 mice were fed a diet containing 167 ppm Aroclor® 1016 for 3, 6, 13, 24 or 40 weeks. Aroclor® 1016 did not consistently alter lymphocyte function but did produce transient alteration. Silkworth and Loose (1188) suggested that Aroclor® 1016 did not interfere with the effector phase of the cell-mediated immune response but implicated the B-cells as possible target cells in PCB-induced humoral immunotoxicity. The PCB-altered humoral immunity also may indicate that PCBs can express selective toxicity on different portions of the immune system, with a more profound influence exhibited by antibody-mediated immunity than cell-mediated immunity.

Byrne et al. (3094) found that Aroclor® 1016, 1242 and 1254 caused profound reductions in circulating adrenal cortex hormones in female Sprague-Dawley rats following exposure to low doses in food (1, 5, 10 or 50 ppm) for 5 or more months. Reduced adrenal weights suggested adrenal toxicity.

Aroclor® 1242

McNulty (1183) reported results from feeding rhesus monkeys 3-800 ppm Aroclor® 1242 for 27-245 days. The first signs of toxicity were usually decreased activity and depressed appetite. The face became swollen and the eyelids were red and puffy. A fine papular roughening of the skin appeared on the face, trunk and extremities and body hair was lost in an irregular fashion. Overall weight loss was as much as 35% before animals became profoundly depressed and died. Autopsy revealed mucous metaplasia of the gastric mucosa and squamous metaplasia of the sebaceous glands. Atrophy of the thymus gland was also seen and in some cases the cortical thymocytes almost completely disappeared. The liver was enlarged, but hepatocytes appeared normal. Since these changes occurred 6-13 months after a short, high level exposure (level not specified) to Aroclor® 1242, McNulty speculated that the pathological effects of PCBs persist until the stored PCBs are finally metabolized and excreted. Thirteen months after a 40-day exposure to dietary Aroclor® 1242, cysts of the mandible and maxilla were still present. These cysts are thought to form when the specialized enamel-secreting epithelium investing the crowns of unerupted teeth is converted to nonkeratinizing desquamating oral epidermis. The castoff squamous cells then create the cysts around the unerupted teeth resulting in severe deformation of the jaw (1184).

As mentioned above, chronic low-level exposure to Aroclor® 1242 caused a reduction in circulating adrenal cortex hormones (3094) in female Sprague-Dawley rats.

Aroclor® 1254

An accidental case of Aroclor® 1254 poisoning occurred in a group of monkeys. Six weeks after being transferred to a newly constructed primate building, 53/249 monkeys died of an unusual form of gastropathy. Autopsies revealed diffuse mucinous gastric hyperplasia. Clinical signs in all affected animals were similar and included diarrhea, weakness, gingivitis, emaciation and dehydration. Alopecia and conjunctivitis were also frequently observed. An additional 32 monkeys exhibited these clinical signs before death, but no gastric hyperplasia. Anorexia and respiratory distress occurred frequently in these animals. When gastric hyperplasia did occur, it usually lasted 4-8 weeks and did not respond to any type of treatment. Microscopic evaluation of the affected areas revealed glandular hyperplasia and cysts. Analysis of tissue revealed Aroclor® 1254 present in the liver and adipose tissues at up to 14 ppm. It was later discovered that paint and concrete samples from the primate housing unit contained 25 ppm Aroclor® 1254 and was the cause of the illness. Once the animals were removed from the PCB source, they began to recover (1167).

Miniats et al. (1168) studied the effects of Aroclor® 1254 in germ-free Yorkshire piglets fed 12.5, 25, 50 or 100 mg/kg Aroclor® 1254 daily until death. Clinical signs of toxicity included hepatitis, focal hepatic necrosis and cirrhosis, acute nephritis and nephrosis, erosion of the gastric mucosa, degeneration of the skeletal muscles and myocardium and lesions in the brain.

Byrne et al. (3093) fed female Sprague-Dawley rats 0, 1, 5, 10 or 50 ppm in the diet for 5-7 months. Serum T3 and T4 levels in the thyroid were suppressed in a dose-dependent fashion, primarily as a result of direct damage to the thyroid. Byrne et al. (3094) also reported reductions in circulating adrenal cortex hormones in rats following chronic low-level exposure to Aroclor® 1254, as discussed above under Aroclor® 1016.

Aroclor® 1260

Vos and Beems (1278) studied the effects of Aroclor® 1260 applied to rabbit skin. One mL of 118 mg PCB-containing solution was dropped daily, 5 times a week for 38 days onto the shaved backs of female New Zealand rabbits. Microscopic examination of the Aroclor® 1260 treated animals revealed hyperplasia and hyperkeratosis of the follicular epithelium with the formation of comedo-like structures. These resulted from the plugging of the dilated hair follicles with keratin. Necroscopy of all animals that died or were killed on day 38 revealed a significant increase in liver and kidney weight. Liver lesions were present in all treated animals with periportal fibrosis being a common finding. Kidney damage was also found in all treated animals. Hydropic degeneration of the convoluted tubules was present in half of the animals while nuclear pycnosis (a thickening, structureless mass) and lyses of the tubular epithelial cells was present in all animals. There was a reduction in the number of germinal centers in the spleen and lymph nodes and atrophy of the thymus in the PCB-treated animals indicating an immunosuppressive effect. Vos and Beems

concluded that PCBs are readily absorbed by the skin in quantities capable of causing similar systemic lesions of the liver, kidney and lymphoid tissue as seen during ingestion of PCBs.

52.3.2 Human and Epidemiologic Studies

52.3.2.1 Short-term Toxicologic Effects

PCBs are slowly metabolized compounds and toxic symptoms usually occur only after long-term exposure and bioaccumulation.

There are no data available on short-term human exposure to any of the Aroclor® congeners.

52.3.2.2 Chronic Toxicologic Effects

Adverse reproductive effects have been reported in female workers exposed to PCBs (3703). The study is discussed in Section 52.3.1.3.

52.3.2.2.1 Yusho

The most notable example of the possible effects of PCB exposure in humans is the Yusho incident which occurred in Japan in 1968. Kaneclor® 400 (48% Cl) inadvertently leached into a commercial rice oil preparation. After a latent period of 5-6 months, symptoms began to manifest. It was initially estimated that the oil was contaminated with 1000-3000 ppm PCBs but reanalysis revealed the presence of 968 ppm PCBs and 8 ppm polychlorodibenzofurans (PCDFs). The majority of people consumed about 200 µg/kg/day. Early symptoms of Yusho (literally "oil disease"), included enlargement and hypersecretion of the meibomian gland of the eye, swelling of the eyelids, pigmentation of the fingernails and mucous membranes, fatigue and nausea. These symptoms were followed by hyperkeratosis, darkening of the skin with follicular enlargement, acneform eruptions with secondary staphylococcal infection, edema of the arms and legs and bronchitis-like respiratory symptoms which persisted for years (1174).

As dermal and mucosal conditions improved after a few years post-exposure, evidence of various systemic disturbances became apparent. Most victims displayed neurological symptoms (e.g., headache, numbness in the limbs, hypesthesia and neuralgic limbs). CNS damage was not apparent. A significant positive correlation was noted between PCB blood levels in Yusho victims and the severity of dermal lesions, ocular symptoms, elevated serum triglyceride concentrations, limb paresthesia and other symptoms (1178).

The majority of Yusho victims complained of persistent cough, sputum production and chronic bronchitis-like symptoms. Secondary respiratory infections were often noted, although no fever and little change in leucocyte count or erythrocyte sedimentation rate was seen (1280). Examination of 400 Yusho patients

revealed respiratory symptoms including expectoration in 40% and wheezing in 2% of 289 non-smokers; the former (along with persistent coughing) appeared with the development of skin eruptions, while the latter appeared several months later. Other respiratory symptoms included bronchiolitis in many, and pneumonia or atelectasis in about 10% of the patients. The incidence and severity of the respiratory symptoms correlated well with the concentration of PCB in the blood and sputa. Viral or bacterial infection increased the severity of the respiratory symptoms and persisted in patients with blood PCB levels over 10 ppb.

Examination of organs of deceased Yusho victims revealed high levels of PCDFs. Liver and adipose tissue samples of Yusho patients revealed 2-25 and 6-13 ppb PCDFs, respectively, while no PCDFs were detected in unexposed volunteers. PCDFs were also shown to be retained in the body, particularly in the liver, much longer than PCBs. In fact, 2, 3, 4, 7, 8-penta-CDF was still present in the tissue of a patient 9 years after the poisoning incident (1174).

The ability of PCBs to cross the placenta and affect the fetus was evident in babies born to Yusho mothers. Of the 12 infants born in 1968 to 11 Yusho mothers and 2 non-Yusho women with Yusho husbands, 10 infants lived and 2 were stillborn. All infants had eye discharge. Nine of the ten live infants had dark grayish skin and 5 had grayish pigmentation of the gums and nails. One of the stillborn fetuses had marked hyperkeratosis, atrophy of the epidermis and cystic dilation of the hair follicles. Also, an increase in melanin pigment was present in the blood cells and the epidermis. All newborns were small and the growth rate of the 10 infants was significantly slower than unaffected children. Teeth were erupted at birth and there was spotted calcification of the parieto-occipital skull, wide fontanels and sagittal suture along with facial edema and exophthalmic eyes (1192).

Miller (1199) also reviewed the effects of PCBs on infants of exposed mothers. A deep brown pigmentation of the skin (usually referred to as cola-colored skin) was the most prevalent symptom. Biopsy of the skin showed an increase in melanin and hyperkeratosis. The pigmentation cleared up within 2-5 months. Low birth weights were also a primary effect of PCB toxicity. The majority of infants had a thick white discharge from the eye and cysts of the meibomian gland. Some of the children exhibited severely swollen eyelids and facial edema. Gingival hyperplasia and teeth present at birth occurred in 16% of the infants investigated. The children with gum overgrowth and natal teeth eruption also had spotty calcification in the occipital region of the skull and a wide separation of the sagittal suture and large anterior and posterior fontanels (membrane covering the unossified space in the skull). These symptoms suggest an irregular calcification which may explain the large unossified areas of the brain and the reduced resistance of the mandible to erupting teeth.

52.3.2.2.2 Yu-Cheng

An incident similar to Yusho was reported in Taiwan in 1979 following consumption of rice oil contaminated with PCBs. The resulting disease was called

Yu-Cheng (oil disease). Symptoms included acneform eruptions and follicular accentuation, pigmentation of the skin and nails, swelling of the eyelids and eye discharge, headache, nausea and numbness of the limbs. Blood disorders included a decrease in red blood cells, an increase in white blood cells and a decrease in hemoglobin and gamma-immunoglobin (1178).

Chang et al. (1281) measured B-cells to evaluate effects on humoral immunity and T-cells to test for effects on cell-mediated immunity in Yu-Cheng patients. Thirty patients were studied with an average blood PCB level of 45 ppb. PCB poisoning did not affect the total lymphocyte count or the number of B-cells. Suppressor T-cells were not affected, but helper T-cells were significantly decreased in Yu-Cheng patients (26.1% vs. 36.9% helper T-cells in control subjects) indicating a range in sensitivity of different lymphocytes to PCBs. Chang et al. concluded that cell-mediated immunity, as shown by decreased T-cell levels, was significantly correlated with PCB toxicity.

Chen et al. (1176) found that the severity of neuropathy was related to the concentration of PCB and PCB derivatives in the blood. The average blood level of PCB in 110 Yu-Cheng victims was 39 ppb. Sensory and motor nerve conduction velocities were shown to be significantly slower in PCB-intoxicated patients.

52.3.2.2.3 Occupational Exposure

Occupational exposure to PCBs presents a different clinical picture. The symptoms most commonly observed appear to be dermal and mucosal effects but no consistent disturbances in liver function. An investigation of former capacitor workers was presented by Lawton et al. (1175). Exposure to PCBs occurred between 1954-1977 when Aroclor® 1242 and 1016 were used extensively. Air levels were estimated to be at least 690 $\mu g/m^3$ dermal contact also occurred. An 80% clearance of the lower chlorinated PCBs was noted in workers re-examined 29 months after exposure had ceased. Traces of highly chlorinated PCBs were found in the blood of long-time workers, particularly those exposed to Aroclor® 1254 before its use was discontinued in 1954. In 1976, blood levels of this compound were 8 ppm. By 1979, 25 years after exposure was discontinued, blood levels were 6 ppm. There was also a statistically significant association of log serum triglycerides and total cholesterol with every measure of log serum PCBs.

Smith et al. (1177) investigated cholesterol and triglyceride levels in PCB-exposed workers and the possible correlation to cardiovascular effects. Two-hundred twenty-eight employees of an electrical equipment manufacturing plant were evaluated. From 1959 to 1971, Aroclor® 1242 was used; Aroclor® 1016 was used thereafter. Forty-seven employees from a public utility plant were also evaluated, 14 of which worked in transformer maintenance. Another 46 employees of a private utility company, 15 working in transformer maintenance and 10 who worked in transformer overhaul, were included. Serum log PCBs correlated significantly with symptoms of mucous membrane and skin irritation, of systemic malaise and of altered

peripheral sensation. Serum log PCBs was also correlated with serum (SGOT), plasma log (triglycerides) and log high density lipoprotein which indicate an effect on liver metabolism and possible development of cardiovascular disease.

Aroclor® 1016

Five employees (1275) of a capacitor manufacturing plant, exposed to Aroclor® 1016 for at least 2 years, were evaluated for possible effects of PCBs. Clinical examination revealed no signs suggestive of PCB toxicity except for occasional reports of skin or mucous membrane irritation upon direct contact with PCB oil or fumes. Blood, liver and kidney function tests were all normal.

Aroclor® 1242

The half-life of serum Aroclor® 1242 was investigated by Steele et al (1172). Examination of 114 people tested for PCB levels in their blood in 1977 were retested in 1984. Results indicated a rapid decrease (of the lower chlorinated Aroclor® 1242) compared to the highly chlorinated PCBs. Assuming no further exposure after the 1977 testing, the half-life for Aroclor® 1242 was estimated to be 6-7 months. Since Aroclor® 1242 was still detected in 1984 at low levels. Steele et al. concluded that people were continuously exposed to low levels of PCBs through environmental background exposure.

An examination of workers occupationally exposed to Aroclor® 1242 was conducted by Ouw et al. (1185). One group of employees dipped capacitor casings directly into a vat of hot Aroclor® 1242. Exposure of this group was excessive with both inhalation and dermal absorption. A second group of employees assembled the Aroclor®-dipped capacitor components which resulted in skin absorption. A control group was included in the study and consisted of volunteers with no history of exposure to PCBs. Exposed workers complained of a burning sensation of the eyes, face and skin, and a persistent body odor. One worker developed chloracne while 5 others complained of eczematous rashes on the hands and legs. Workers dipping the capacitor casings in Aroclor® 1242 absorbed the more volatile compounds while workers exposed to PCBs during the assembly of the PCB-dipped components absorbed the heavier compounds. Blood Aroclor® 1242 levels ranged from 313-602 ppb for the group of workers dipping the capacitor casings and 100-899 ppb for the group assembling the components. Some individual abnormal results occurred in the liver function test; however, overall. the group was within normal limits. Aroclor® 1242 is known to penetrate human skin which results in a significant source of exposure. This would account for the high blood level seen in the group of workers dermally exposed during assembly of the capacitors.

Blood PCB levels of mothers occupationally exposed in a capacitor manufacturing plant, and their children, were analyzed from 1975 to 1979. The commercial PCBs handled were equivalent to Aroclor® 1242 and 1254. Blood PCB levels were 10 to 100 times higher than that of non-occupationally exposed persons (3385). There was

little correlation between blood levels in the mothers and their offspring; however, concentrations of PCBs in the blood of the children was influenced greatly by the duration of breast feeding (3854). Body weight and height of the children was not significantly different from the children of nonexposed mothers. However, there was an increase in the number of complaints of red eye, itchy skin, fever and carious teeth in children breast-fed for over 5 months. Typical symptoms identified in Yusho patients (i.e., decay of nails, pigmentation and mottled enamel) were observed in some of the children, but not diagnosed as a result of PCB poisoning.

Aroclor® 1254

A slight increase in the incidence of cancer, particularly melanoma of the skin, has been reported in a small group of men occupationally exposed to Aroclor® 1254. Eight cancers (in 7 workers) were reported between 1957 and 1975 in 92 workers exposed to Aroclor® 1254. Of these eight cancers, 3 were malignant melanoma and 2 were cancer of the pancreas. Data from the NCI estimate that 0.04 malignant melanomas should be expected to develop in this group. These data suggest a possible correlation between Aroclor® 1254 and the development of malignant melanomas. Exposure to other chemicals was not known (1457, 1459).

Yakushiji et al. (3854) reported a correlation between health effects seen in offspring of Aroclor® 1254-exposed mothers and duration of breast feeding (see section above on Aroclor® 1242).

Aroclor® 1260

The half-life of serum Aroclor® 1260 was investigated by Steele et al. (1172), as discussed in the section on Aroclor® 1242. The estimated half-life of Aroclor® 1260 was 33-34 months.

Fifty-five present and past transformer repair workers exposed primarily to Aroclor® 1260 and 56 unexposed workers were evaluated in a clinical epidemiologic study (3199). Adipose tissue lipid and serum PCB concentrations were found to be significantly higher in the currently exposed group than in the previously or non-exposed groups. Statistical differences were found in serum albumin and lactic dehydrogenases between the currently exposed and comparison groups. However, after adjustment for confounding variables, no correlation was found between any liver function tests and adipose or serum PCB concentrations. Lees et al (1987 - L52-10) in a companion study determined that dermal absorption rather than inhalation was the principal route of exposure for the transformer repair workers investigated by Emmett et al (3199).

52.3.3 Levels of Concern

The EPA has established long-term drinking water health advisories for PCBs of 1 μg/L and 4 μg/L for the 10-kg child and 70-kg adult, respectively (3742). Since

PCBs are classed as Group 2B carcinogens by EPA, they have also established a 1E-04 cancer risk level of 0.5 μg/L of drinking water. Risk estimates are expressed as a probability of cancer after a lifetime consumption of two liters of contaminated water per day. Thus, a risk of 1E-04 implies that a lifetime daily consumption of two liters of drinking water at the level of 0.5 μg/L PCBs would be expected to produce one excess case of cancer above the normal background incidence for every 10,000 people exposed. It should be emphasized that these extrapolations are based on a number of assumptions and should be taken as crude estimates of human risk at best.

EPA has proposed an MCLG of zero μg/L and an MCL of 0.5 μg/L for PCBs in drinking water.

OSHA (3539) currently permits exposure to between 0.5 mg/m³ (54% Cl) and 1 mg/m³ (42% Cl) with a notation of potential skin absorption. The ACGIH (3005) originally recommended identical exposure limits as OSHA and listed short-term exposure limits of between 1 mg/m³ (54% Cl) to 2 mg/m³ (42% Cl); however, STELS for 54% Cl and 42% Cl have been subsequently deleted by ACGIH.

52.3.4 Hazard Assessment

In that commercial preparations of PCBs are complex mixtures of several isomers, assessment of hazard for the various congeners is confounded by a number of factors. Not only dose, but also the dose-time relationship are important determinants of effect; a lesser amount of PCBs may be able to produce a given level of intoxication, if exposure is extended. In addition, considerable species sensitivity to the same PCB formulation has also been noted.

In acute, relatively high-dose studies with most species, the first sign of intoxication is usually weight loss or reduced weight gain, which is only partially due to a decrease in food or water consumption. Severely poisoned rats have exhibited ataxia, diarrhea and lack of response to pain stimuli. Death was most likely caused by progressive dehydration and CNS depression (1279). The median time to death is usually 2 to 3 weeks for small laboratory animals. Oral LD_{50} values in rats range from 4000 to 10,000 mg/kg, with toxicity generally decreasing with increased chlorination (1178).

The most consistent pathological changes observed in most mammalian species after PCB exposure have been alterations in the liver. Liver enlargement has been noted even in those species in which actual liver lesions were minimal (such as monkeys) and at doses below which other effects, such as reduced thymus weights, were observed. Investigators suggest that the liver enlargement may be due to hepatocellular hypertrophy (1164).

Chronic oral exposure studies in rodents indicated Aroclor® 1254 to be carcinogenic in mice and Aroclor® 1260 to be carcinogenic in rats, inducing benign

and malignant liver tumors (1283, 1193, 1194, 1169, 1170, 1171). There are no data for Aroclor® 1016 or Aroclor® 1242. There is also suggestive evidence of the development of malignant melanoma in humans exposed to Aroclor® 1254 (1457, 1459).

Mutagenicity data are inadequate to establish a clear picture of mutagenic activity for these compounds. Negative findings have been reported for Aroclor® 1242 in mammalian cells (1180, 1181) as well as in a dominant lethal test in rats (1182). Aroclor® 1254 gave negative results in cultured human lymphocytes (1457), in bacterial tests (1251) and in a rat dominant lethal study (1457). A single report on Aroclor® 1260 provided negative results in a dominant lethal test (2). No data were found for Aroclor® 1016.

A number of studies have indicated that PCB exposure has a notable depressive effect on reproductive capacity and fetal survival (1196, 1197, 1460, 1160, 3042). Exposure of rats to PCBs during the prenatal period resulted in changes in sexual development in females (1162, 1161) and reduced reproductive function in males (1163). Indications of structural malformations or other teratogenic effects, however, have been few (1016); most oral exposure studies have been negative.

Humans appear to be among the most sensitive species to PCBs. The most notable example is the Yusho incident which occurred in Japan in 1968. Initial symptoms of PCB poisoning were non-specific, including general fatigue, gastrointestinal disturbances, weakness, spasms and hearing and visual disturbances. The most common specific symptoms were dermal and mucosal effects, including acneform eruptions, hyperpigmentation (especially of the face, eyelids, nails and gingivae), cystic dilation of the hair follicles and hyperkeratosis. Severe ocular manifestations were also evident in the acute phase of the disease, the most notable being hypersecretion of the meibomian glands causing swelling of the upper eyelids and abnormal pigmentation of the conjunctiva (1174).

Developmental abnormalities were observed in several Yusho babies, including premature eruption of teeth, larger frontal and occipital fontanels and maintenance of an abnormally wide sagittal suture. Spotted and sporadic ossification of the skull and facial edema with exophthalmia were also reported. No other obvious malformations were evident (1192, 1199).

Women occupationally exposed to high concentrations of Aroclor® 1016, Aroclor® 1242 and Aroclor® 1254 were observed to give birth to infants with reduced birth weight even after adjustment for year of birth, maternal parity and sex of infant. Mean gestational age was reduced by 6.6 days when compared to a low exposure group (3703) Another set of women occupationally exposed to PCBs reported an increase in the number of complaints of red eye, itchy skin, fever and carious teeth in children breast-fed for over 5 months (3854).

The USEPA (3879) considers the PCBs to be a Class 2B carcinogen and has calculated an upper-limit incremental unit cancer risk of 7.7 $(mg/kg/day)^{-1}$ for PCBs.

52.4 SAMPLING AND ANALYSIS CONSIDERATIONS

Determination of the concentrations of the various Aroclor congeners (1254, 1260, 1242 and 1016) in soil and water requires collection of a representative field sample and laboratory analysis. Care is required to prevent losses during sample collection and storage. Soil and water samples should be collected in glass containers; extraction of samples should be completed within 7 days of sampling and analysis completed within 40 days. In addition to the targeted samples, quality control samples such as field blanks, duplicates and spiked matrices may be specified in the recommended methods.

EPA-approved procedures for the analysis of Aroclor congeners, EPA priority pollutants, in aqueous samples include EPA Methods 608, 625 (65), 8080 and 8250 (63). Prior to analysis, samples are extracted with methylene chloride as a solvent using a separatory funnel or a continuous liquid-liquid extractor. The concentrated sample extract is solvent exchanged into hexane and an aliquot of the hexane extract injected onto a gas chromatographic (GC) column using a solvent flush technique. The GC column is programmed to separate the semi-volatile organics; Aroclor congeners are then detected with an electron capture detector (Methods 608 and 8080) or a mass spectrometer (Methods 625 and 8250). Aroclors have also been concentrated in water samples for analysis by GC/ECD by using C18 cartridges (3714). The sample is passed through the cartridge and retained PCBs are eluted with organic solvents.

The EPA procedures recommended for Aroclor analysis in soil and waste samples, Methods 8080 and 8250 (63), differ from the aqueous procedures primarily in the preparation of the sample extract. Solid samples are solvent extracted using either soxhlet or sonication methods. Neat and diluted organic liquids may be analyzed by direct injection.

Typical detection limits that can be obtained for the Aroclor congeners in waste waters and non-aqueous samples (wastes, soils, etc.) are shown below. The actual detection limit achieved in a given analysis for a given Aroclor will vary with instrument sensitivity and matrix effects. (Aroclor congeners are mixtures of isomers; multiple peaks are used for quantification.)

Aqueous Detection Limit	Non-Aqueous Detection Limit
0.065 µg/L PCB 1242 (Method 608)	0.042 µg/g PCB 1242 (Method 8080)
0.65 µg/L PCB 1242 (Method 8080)	
36 µg/L PCB 1254 (Method 625)	

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Note: The nonsequential numbers of the references reflect the order of references as they appear in the master bibliography.

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COMMON SYNONYMS:	CAS REG.NO.: FORMULA:	AIR W/V CONVERSION FACTOR at 25°C (12)
Chromate of soda Chromic acid, disodium salt Disodium chromate Sodium chromate	7775-11-3 $CrO_4 \cdot 2NA$ NIOSH NO: GB2955000 MOLECULAR WEIGHT: 161.97	6.62 mg/m³ ≈ 1 ppm; 0.15 ppm ≈ 1 mg/m³

REACTIVITY	Sodium chromate is an oxidizing agent that may cause fire in contact with combustible materials. One source explains that it is mildly oxidizing in water solutions and highly oxidizing in strong acid solutions, thus requiring separation from organic materials, oils, greases, and any other oxidizing materials. Others list strong alkalies and strong acids as incompatible as well as combustible, organic, or other readily oxidizable materials such as paper, wood, sulfur, aluminum, plastics, etc. The NFPA notes that chromates in general may cause explosive decomposition of hydrazine. Compatibility charts indicate incompatibility with all types of organic or combustible materials (54, 60, 505, 507, 511).

PHYSICO-CHEMICAL DATA	• Physical state: Solid, crystalline (at 20°C)	(507)
	• Color: Yellow	(507)
	• Odor: None	(507)
	• Odor Threshold: Not pertinent	
	• Density: 2.723 g/mL (at 20°C)	(59)
	• Freeze/Melt Point: 792.0°C	(59)
	• Boiling Point: Decomposes	(507)
	• Flash Point: Nonflammable	(507)
	• Flammable Limits: Nonflammable	(507)
	• Autoignition Temp.: Nonflammable	(507)
	• Vapor Pressure: Not pertinent	
	• Satd. Conc. in Air: Not pertinent	
	• Solubility in Water: 8.73E+03 mg/L (at 30°C)	(59)

PHYSICO-CHEMICAL DATA (Cont.)	• Viscosity: Not pertinent • Surface Tension: Not pertinent • Log (Octanol-Water Partition Coeff.): Not pertinent • Soil Adsorp. Coeff.: Not pertinent • Henry's Law Const.: Not pertinent • Bioconc. Factor: Not pertinent
PERSISTENCE IN THE SOIL-WATER SYSTEM	Sodium chromate, as aqueous Na^+ and CrO_4^{-2}, is expected to be relatively mobile in soil. However, protonation of CrO_4^{-2} to $HCrO_4^-$ (the predominant species at pH < 6.5) decreases its mobility, and reduction to relatively immobile trivalent forms of chromium occurs readily in soils with sufficient organic matter. pK_1=0.74, pK_2=6.49.
PATHWAYS OF EXPOSURE	Exposure via ingestion of contaminated drinking water is the most likely route for chromate; volatilization from contaminated sources is not important. Other forms of chromium are found at trace levels in air and certain foods.
HEALTH HAZARD DATA	Signs and Symptoms of Short-term Human Exposure: (54) Cr(VI) dust or mist may cause coughing and wheezing, headache, dyspnea, pain on deep inspiration, fever and loss of weight. Local contact can result in dermatitis, skin ulcers and perforated nasal septa.

HEALTH HAZARD DATA (Cont.)	Acute Toxicity Studies: INHALATION: LC_{50} 104 mg/m³ Rat (507) ORAL: LD_{50} 50 mg/kg Rat (47) SKIN: LD_{50} 1600 mg/kg Rabbit (507) Long-Term Effects: Kidney damage, dermatitis Pregnancy/Neonate Data: Teratogenic and fetotoxic in hamsters increasing with dose; and maternal toxicity at high doses Genotoxicity Data: Sufficient evidence. Carcinogenicity Classification: IARC - Group 1 (carcinogenic to humans); (for Chromium(VI) and its cmpds) NTP - Studies in progress EPA - Chromium (VI) Group A (Human Carcinogen) by inhalation

HANDLING PRECAUTIONS	Handle chemical only with adequate ventilation • Concentrations <5 mg/m³: any dust and mist respirator • 5-10 mg/m³: any dust and mist respirator, except single-use or quartermask respirator or any fume respirator or high efficiency particulate respirator or any supplied-air respirator or any self-contained breathing apparatus • 10-50 mg/m³: a high efficiency particulate filter respirator with a full facepiece or any supplied-air respirator with full facepiece, helmet or hood or any self-contained breathing apparatus with a full facepiece • 50-500 mg/m³: a powered air-purifying respirator with a high efficiency particulate filter or a Type C supplied-air respirator operated in pressure-demand or other positive pressure or continuous-flow mode • Chemical goggles if there is a probability of eye contact • Protective clothing

ENVIRONMENTAL AND OCCUPATIONAL STANDARDS AND CRITERIA

AIR EXPOSURE LIMITS:

Standards
- OSHA TWA (8-hr): chromic acid and chromates (as CrO_3) - ceiling 0.1 ppm
- AFOSH PEL (8-hr TWA): chromic acid and chromates (as CrO_3) - ceiling 0.1 ppm

Criteria
- NIOSH IDLH (30-min): chromic acid and chromates (as CrO3) - 30 mg/m³
- NIOSH REL: no data
- ACGIH TLV® (8-hr TWA): Water soluble chromium (VI) compounds - 0.05 mg/m³ (as Cr)
- ACGIH STEL (15-min): none established

WATER EXPOSURE LIMITS:

Drinking Water Standards
For total chromium:
MCL (interim): 0.05 mg/L (3800)
MCLG (proposed): 0.1 mg/L (3883)
MCL (proposed): 0.1 mg/L (3883)

EPA Health Advisories and Cancer Risk Levels (3977)
The EPA has developed the following Health Advisories for total chromium which provide specific advice on the levels of contaminants in drinking water at which adverse health effects would not be anticipated.

- 1-day (child): 1.0 mg/L
- 10-day (child): 1.0 mg/L
- longer-term (child): 0.2 mg/L
- longer-term (adult): 0.8 mg/L
- lifetime (adult): 0.1 mg/L

WHO Drinking Water Guideline (666)
A health-based guideline for drinking water of 5 µg/L is recommended for total chromium. A daily per capita consumption of two liters of water was assumed.

EPA Ambient Water Quality Criteria
- Human Health (355,1777)
  - The ambient water quality criterion for total chromium (VI) is recommended to be identical to the drinking water standard of 0.05 mg/L of chromium.

ENVIRONMENTAL AND OCCUPATIONAL STANDARDS AND CRITERIA (Cont.)

- Aquatic Life (355, 1777)
  - Freshwater species
    Freshwater aquatic organisms and their uses should not be affected unacceptably if the four-day average concentration of chromium (VI) does not exceed 11 μg/L more than once every 3 years on the average and if the 1 hour average concentration does not exceed 16 μg/L more than once every 3 years on the average. Freshwater aquatic organisms and their uses should not be affected unacceptably if the four-day average concentration (in μg/L) of chromium (III) does not exceed the numerical value given by e(0.8190[ln(hardness)])+1.561 more than once every 3 years on the average and if the 1 hour average concentration (in μg/L) does not exceed the numerical value given by e(0.8190[ln(hardness)])+3.688 more than once every 3 years on the average.

  - Saltwater species
    Saltwater aquatic organisms should not be affected unacceptably if the four-day average concentration of chromium (VI) does not exceed 50 μg/L more than once every 3 years on the average and if the 1 hour average concentration does not exceed 1100 μg/L ore than once every 3 years on the average. No saltwater criterion can be derived for chromium (III), but 10,300 μg/L is the EC_{50} for eastern oyster embryos, whereas 50,400 μg/L did not affect a polycheate worm in a life-cycle test.

REFERENCE DOSES: (3744)
For total chromium: 5 μg/kg/day

REGULATORY STATUS (as of 01-MAR-89)

Promulgated Regulations

- Federal Programs

Clean Water Act (CWA)

Sodium chromate and sodium dichromate are designated as hazardous substances. They have a reportable quantity (RQ) limit of 454 kg (747, 3764). Chromium and chromium compounds are listed as toxic pollutants, subject to general pretreatment regulations for new and existing sources, and effluent standards and guidelines (351, 3763). Effluent limitations exist for effluent containing hexavalent chromium in the petroleum refining and the ferroalloy manufacturing point source categories (896, 895). Limitations exist for total chromium in the following point source categories: leather tanning and finishing (1437), textile mills (893), petroleum refining (896), inorganic chemicals manufacturing (896), steam electric power generating (3802), ferroalloy manufacturing (895), nonferrous metals manufacturing (894), organic chemicals, plastics, and synthetic fibers (3777), iron and steel manufacturing (354), timber products processing (899), and metal finishing (3768). Limitations vary depending on the type of plant and industry.

Safe Drinking Water Act (SDWA)

Chromium is on the list of 83 contaminants required to be regulated under the SDWA of 1974 as amended in 1986. Under the National Primary Drinking Water Regulations, the maximum contaminant level (MCL) for chromium is 0.05 mg/L. This MCL applies to community water systems which serve a population of 10,000 people or more and which add a disinfectant as part of their treatment process (3800). In states with an approved Underground Injection Control program, a permit is required for the injection of chromium-containing wastes designated as hazardous under RCRA (295).

Resource Conservation and Recovery Act (RCRA)

Chromium compounds are listed as hazardous waste constituents (3783). Non-specific sources of hexavalent chromium-containing wastes are wastewater treatment sludges from the chemical conversion coating of aluminum and from electroplating operations (325, 3765). Waste streams from the following industries contain hexavalent chromium and are listed as specific sources of hazardous wastes: inorganic pigments, petroleum refining, iron and steel, secondary lead, and ink formulation (3774, 3765). Total chromium is included on EPA's groundwater monitoring list. EPA requires that all hazardous waste treatment, storage, and disposal facilities monitor their groundwater for chemicals on this list when suspected contamination is first detected and annually thereafter (3775). For groundwater protection, the maximum concentration of chromium-containing hazardous waste in groundwater is 0.05 mg/L (989). Solid wastes are listed as hazardous because they exhibit the characteristic defined as EP toxicity when the TCLP extract concentration is equal to or greater than 5 mg/L chromium (988). Effective July 8, 1987, land disposal of untreated liquid hazardous

wastes, including free liquids associated with any solid or sludge containing hexavalent chromium and/or its compounds at concentrations greater than or equal to 500 mg/L is prohibited. Effective August 8, 1988, the underground injection into deep wells of these wastes is prohibited. Certain variances exist until May, 1990 for land and injection well disposal of some wastewaters, nonwastewaters, and soils for which Best Demonstrated Available Technology (BDAT) treatment standards have not been promulgated by EPA (3786). Used oil that is burned for energy recovery may not contain greater than 10 ppm chromium (1768).

Comprehensive Environmental Response Compensation and Liability Act (CERCLA)
Sodium chromate is designated a hazardous substance under CERCLA. It has a reportable quantity (RQ) limit of 454 kg. Reportable quantities have also been issued for RCRA hazardous waste streams containing sodium chromate but these depend upon the concentrations of the chemicals in the waste stream (3766).

Marine Protection Research and Sanctuaries Act (MPRSA)
Ocean dumping of organohalogen compounds as well as the dumping of known or suspected carcinogens, mutagens or teratogens is prohibited except when they are present as trace contaminants. Permit applicants are exempt from these regulations if they can demonstrate that such chemical constituents are non-toxic and non-bioaccumulative in the marine environment or are rapidly rendered harmless by physical, chemical or biological processes in the sea (309).

Occupational Safety and Health Act (OSHA)
Chromic acid and chromates have a ceiling level of 0.1 ppm which should not be exceeded at any time during an 8-hour work-shift (3539).

Hazardous Materials Transportation Act (HMTA)
The Department of Transportation has designated sodium chromate as a hazardous material with a reportable quantity of 454 kg, subject to requirements for packaging, labeling and transportation (3180).

Food, Drug and Cosmetic Act (FDCA)
Sodium chromate is approved for use as an indirect food additive (3209). The level for chromium in bottled drinking water is 0.05 mg/L. This level is identical to the maximum contaminant level (MCL) given under the Safe Drinking Water Act (365).

- State Water Programs

  ALL STATES
  All states have adopted EPA Ambient Water Quality Criteria and NPDWRs (see Water Exposure Limits section) as their promulgated state regulations, either by narrative reference or by relisting the specific numeric criteria. These states have promulgated additional or more stringent criteria:

GEORGIA
Georgia has a water quality standard for total chromium of 120 μg/L (at hardness levels less than 100 mg/L) in all waters (3240).

VERMONT
Vermont has a prevention action limit of 25 μg/L and an enforcement standard of 50 μg/L for chromium in groundwater (3682).

WISCONSIN
Wisconsin has a preventive action limit of 5 μg/L and an enforcement standard of 50 μg/L for chromium in groundwater (3840).

WYOMING
Wyoming has a water quality standard for chromium of 0.1 mg/L for Class II groundwaters (3852).

Proposed Regulations

- Federal Programs

Safe Drinking Water Act (SDWA)
EPA has proposed a maximum contaminant level goal (MCLG) and a maximum contaminant level (MCL) of 0.1 mg/L for total chromium as part of the National Primary Drinking Water Regulations (3883). Final promulgation is scheduled for May, 1990 (3759).

Resource Conservation and Recovery Act (RCRA)
EPA has proposed listing wastestreams from the following industries as non-specific sources of chromium-containing hazardous waste: metal heat treating operations, chlorinated aliphatic hydrocarbon production (325, 3765). EPA has proposed listing wastestreams from the organic chemicals industry (production of 1,1,1-trichloroethane) as specific sources of chromium-containing waste (3774, 3765). EPA has proposed that solid wastes be listed as hazardous in that they exhibit the characteristic defined as EP toxicity when the TCLP extract concentration is equal to or greater than 5.0 mg/L hexavalent chromium. Final promulgation of this Toxicity Characteristic Rule is expected in June, 1989 (1565).

Clean Air Act (CAA)
EPA intends to list chromium as a hazardous air pollutant. Emission standards (NESHAPS) will be proposed in 1990 (1406).

- State Programs

MOST STATES
Most states are in the process of revising their water programs and proposing changes in their regulations which will follow EPA's changes when they become final. Contact with the state officer is advised. Changes are projected for 1989-90 (3683)

EEC Directives

Directive on Drinking Water (533)
The mandatory values for total chromium in surface water treatment categories A1, A2 or A3 are 0.03 mg/L. There are no guideline values.

Directive Relating to the Quality of Water for Human Consumption (540)
The maximum admissible concentration for chromium is 50 mg/L.

Directive on Ground-Water (538)
Direct and indirect discharge of chromium into ground-water shall be subject to prior review so as to limit such discharges.

Directive on Bathing Water Quality (534)
When inspection of a bathing area shows that heavy metals, pesticides or cyanides may be present, concentrations should be checked by competent authorities.

Directive on the Quality Required of Shellfish Waters (537)
The mandatory specifications for chromium specify that the concentration of each substance in the shellfish water or in shellfish flesh must not reach or exceed a level which has harmful effects on the shellfish and larvae. The synergistic effects of other metals must be taken into consideration. The guideline specifications state that the concentration of chromium in shellfish flesh must be so limited that it contributes to the high quality of shellfish product.

Directive on the Discharge of Dangerous Substances (535)
Chromium cannot be discharged into inland surface waters, territorial waters or internal coastal waters without prior authorization from member countries which issue emission standards. A system of zero-emission applies to discharge of these substances into ground-water.

Directive on Toxic and Dangerous Wastes (542)
Any installation, establishment, or undertaking which produces, holds and/or disposes of certain toxic and dangerous wastes including phenols and phenol compounds; organic-halogen compounds; chrome compounds; lead compounds; cyanides; ethers and aromatic polycyclic compounds (with carcinogenic effects) shall keep a record of the quantity, nature, physical and chemical characteristics and origin of such waste, and of the methods and sites used for disposing of such waste.

Directive on the Classification, Packaging and Labeling of Dangerous Substances (787)
Sodium dichromate is classified as an irritant substance and is subject to packaging and labeling regulations.

Directive on Paints, Varnishes, Printing Inks, Adhesives and Similar Products (1334)
Sodium dichromate is classified as an irritant substance when present in concentrations greater than or equal to 0.5%.

Directive on Transfrontier Shipment of Hazardous Waste (1433)
When the holder of a hazardous waste such as chromium intends to ship it to another member state, authorities of the member states concerned must be provided with information on the source and composition of the waste, measures to be taken to ensure safe transport, insurance against damage and the existence of a contractual agreement with the consignee of the waste. All transfrontier shipments must be properly packed and labeled and must be accompanied by instructions to be followed in the event of danger or accident.

Council Directive on the Approximation of the Laws, Regulations and Administrative Provisions Relating to the Classification, Packaging and Labelling of Dangerous Preparations (3991)
Paints and varnishes containing lead quantities exceeding 0.25% as weight of metal and less than 125 millilitres; and glues containing cyanoacrylates must contain labels indicated in Annex II of this directive.

EEC Directives - Proposed
Proposal for a Council Directive on the Dumping of Waste at Sea (1793)
EEC has proposed that the dumping of chromium compounds at sea be forbidden without prior issue of a special permit.

Proposal for a Council Directive on Water Quality Objectives for Chromium (1428)
EEC has proposed that the concentration of dissolved chromium in fresh water be below 5-50 µg/L depending on water hardness. For sea water, the upper limit would be 15 µg/L. The proposal would not regulate chromium in ground-water or drinking water. Implementation of the program would be completed by 15 September 1991.

53.1 MAJOR USES

Sodium chromate (Na_2CrO_4) is used in leather tanning, wood preservation, corrosion inhibition and pigment manufacturing. It is also used as a raw material for production of other chromium compounds such as sodium dichromate ($Na_2Cr_2O_7$) (1252).

53.2 ENVIRONMENTAL FATE AND EXPOSURE PATHWAYS

53.2.1 Transport in the Soil/Ground-water Systems

53.2.1.1 Overview

The high solubility of sodium chromate in water means that the mobility of sodium (Na^+) and chromate (CrO_4^{-2}) must be considered separately when assessing its mobility in the soil/ground-water environment. The sodium ion can be expected to be relatively mobile depending on the soil type and the concentration of other cations competing for soil ion exchange sites. However, the sodium ion is of little environmental significance compared to the chromate ion.

The chromate ion, as such, is expected to be relatively mobile in the soil/ground-water environment (1702). In protonated form ($HCrO_4^-$), the mobility of the ion is decreased. The organic matter in the soil readily reduces chromate (or dichromate) to a trivalent form, either Cr^{+3} or CrO_2^-, which form compounds of much lower solubility than the 2 hexavalent chromates. In soils of low organic matter content, however, bulk quantities of chromate could be transported down through the unsaturated zone, if the sorbing capacity of the soil is exceeded.

The chromate ion can act as a weak base, with a strength close to that of the bicarbonate ion. The acid dissociation constant of $HCrO_4^-$ is E-6.51 (25°C, zero ionic strength) (1704); this indicates that at pH 6.5 half the chromate in solution would exist as $HCrO_4^-$, at pH 5.5, 90% would exist in this form, and at pH 7.5, 9%.

Environmental transport pathways for sodium chromate cannot be assessed using an equilibrium partitioning model as is done for organic chemicals. Because it is an ionic species that readily dissolves into its component ions, sodium chromate is non-volatile. The susceptibility of hexavalent chromium to reduction by organic matter makes partitioning calculations virtually meaningless.

53.2.1.2 Sorption on Soils

The high solubility of sodium chromate in water (37.7 wt % at 15°C (1701)) indicates that reactions involving its precipitation on soils are expected to be relatively unimportant. Except in arid regions, solid Na_2CrO_4 that is deposited on soil will

readily dissolve in atmospheric precipitation. Where this happens, or where spills of aqueous Na_2CrO_4 have occurred, the fate of Na^+ and CrO_4^{-2} must be considered individually. Since the chromate ion is of much greater environmental concern than sodium, most of the discussion below focuses on it.

Sodium sorption on soils occurs primarily by ion exchange (1702). It is relatively weakly retained by soils. Among major monovalent cations (which tend to be less strongly held than multivalent cations), it is just slightly more strongly held than lithium, the most weakly retained ion (1703). The ion exchange of sodium is governed by the laws of mass action at exchange sites (1702) and thus the presence and concentration of other competing cations in the soil water determine its retention.

The transport of chromium introduced as chromate is strongly dependent on the transformations it undergoes, which are described in the following section. As noted above, sodium chromate is highly soluble in water, as are most other chromates. Exceptions are lead chromate ($PbCrO_4$), barium chromate ($BaCrO_4$), and silver chromate (Ag_2CrO_4), with pK_{sp} values, (at 25°C and zero ionic strength) of 12.60, 9.67, and 11.92, respectively (1704). Barium and silver concentrations are too low under environmental conditions to control chromate solubility; however, lead chromate may, under certain conditions, precipitate at pH < 8 if the Pb^{+2} concentration is controlled by $PbSO_4(s)$ (at pH < 6) and $PbCO_3(s)$ (at pH > 6) [(s) = speculated] (1702).

The distribution of chromate between protonated and deprotonated form ($HCrO_4^-$ and CrO_4^{-2}) is dependent on pH. Both forms may be sorbed to soils, although their behavior differs. Chromate may be sorbed like SO_4^{-2} and HPO_4^{-1}, by forming binuclear bridged structures on goethite [Fe.OCr(OO).Fe] or aluminum oxides and other soil colloids having positively charged surfaces, or it may be sorbed by ligand exchange (1705).

Chromium(VI) has also been found to sorb to activated carbon, primarily as $Cr_2O_7^{-2}$ and $HCrO_4^-$ (1708). Chromium(III) was found to be sorbed to a lesser extent. Bichromate, $HCrO_4^-$ (also called hydrochromate), may behave like HPO_4^- and be tightly held in soils or it may act like HCO_3^-, Cl^-, and NO_3^- and remain soluble (1705). In experiments using K_2CrO_4, James and Bartlett (1705) found an average of 36% of the Cr(VI) was removed by 38 soils having a mean pH of 5.4, while 13% was removed from limed soils having a pH of 7. Subsurface B horizon soils were found to remove somewhat more Cr(VI) than A horizon soils. The precise mechanism of chromate removal could not be determined, and thus the relative contributions of Cr(VI) precipitation, sorption and reduction to Cr(III) could not be assessed. Nevertheless, the finding of increased Cr(VI) removal at decreased pH is consistent with the observation that $HCrO_4^-$ is the predominant Cr(VI) species sorbed (1706) since it would be present in increasing concentrations at lower pH's.

Most data on CrO_4^{-2} sorption to soils have been obtained using pure soil minerals rather than actual soil samples (1702). The results of these studies indicate that

minerals with high isoelectric points [e.g., alpha-Al_2O_3, FeO_2H_2O(am), other iron oxides, and (to a lesser extent) clay minerals] adsorb Cr(VI) at pH's of roughly 2 to 7 (1702). The Langmuir adsorption maxima (umol sorbed/gram of soil) for Cr(VI) on two soil minerals using K_2CrO_4 as the electrolyte are given in the following table.

TABLE 53-1
CHROMATE SORPTION

Soil Mineral	Solution pH	Langmuir Maxima µmol/g
Kaolinite	3	1.79
	4	0.85
	5	0.62
	7	0.29
Montmorillonite	3	3.6[illegible]
	4	2.50
	5	2.22
	7	0.98

53.2.1.3 Volatilization from Soils

As an ionic species readily soluble in water, sodium chromate is non-volatile, and thus volatilization from soil is expected to be an insignificant transport pathway.

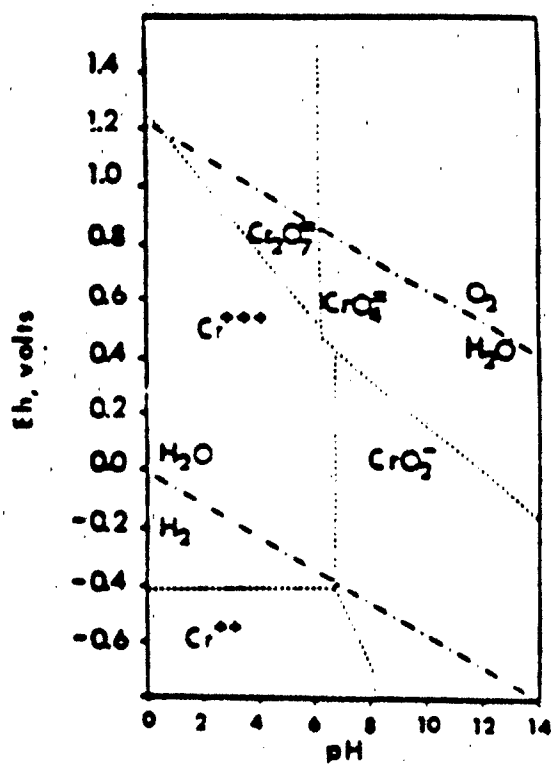
53.2.2 Transformation Processes in Soil/Ground-water Systems

As CrO_4^{-2} and $Cr_2O_7^{-2}$ are hydrolysis products of Cr(VI), neither is further hydrolyzed itself. Reduction of CrO_4^{-2} may be the most important reaction affecting its environmental transport. Its redox behavior is illustrated in Figure 53-1, which shows the predominant form of aqueous chromium over a range of pH and Eh (oxidation reduction potential) conditions.

For water in equilibrium with air at pH 7, the theoretical value of Eh at 25°C is 0.80 volts, and the dependence of Eh on pH and the partial pressure of oxygen P_o can be expressed as (1706):

$$Eh = 1.234 - 0.058\ pH + 0.0145 \log P_o$$

Thus, in well oxygenated waters of intermediate pH, CrO_4^{-2} and $Cr_2O_7^{-2}$, both containing hexavalent chromium, are expected to predominate. At lower pH (and Eh) levels, Cr(VI) is reduced to Cr(III), either as Cr^{+3} or CrO_2^{+}. Figure 53-1 and the discussion above should be taken as descriptions of limiting conditions only.



Source: Bartlett and Kimble (1710)

FIGURE 53-1

Eh-pH DIAGRAM OF Cr SPECIES IN WATER AT 25°C

Often equilibrium conditions are not quickly reached in ground waters, as shown by the work of Lindberg and Runnells (1707).

Hexavalent chromium as $K_2Cr_2O_7$ was found to be spontaneously reduced to Cr(III) by soil organic matter even at pH levels above neutrality (1708). However in soils with very low organic matter content, reduction did not occur until an energy source was added. Thus, in deep saturated soils with little organic matter Cr(VI) would not be expected to be reduced despite a lack of air.

Trivalent chromium species have been found to be oxidized to the hexavalent form in the presence of oxidized forms of manganese (1711). Thermodynamic considerations, based on the addition of half cell reactions for Cr(III) oxidation and Mn reduction, generally favor the formation of Cr(VI) (1711). Chromate that has been reduced to the trivalent form but remains in solution may be reoxidized to hexavalent form if it moves to areas where manganese oxides are present.

The biological transformation of Cr(VI) species (CrO_4^{-2} or $Cr_2O_7^{-2}$) is one of reduction. Cr(VI) readily penetrates cell membranes and is then reduced, its toxicity probably resulting from the oxidation of cell components (1712). Because it is an essential nutrient, chromium is bioaccumulated in many organisms (10, 1713, 1714).

It has been suggested that chromium could be methylated in reducing environments but no evidence that this occurs in natural or experimental systems was found (10). It is also possible that CrO_4^{-2} could be used as an oxygen source for microorganisms under anaerobic conditions, although this process could not be distinguished from the chemical reduction of these species to Cr(III) with the loss of oxygen (10).

53.2.3 Primary Routes of Exposure from Soil/Ground-water Systems

The above discussion of fate pathways suggests that the mobility and potential exposure to sodium chromate is very dependent on the environmental conditions. This compound or its ions are considered to have a low volatility as are the various forms of chromium. The chromate ion is generally expected to be mobile in soils, although other forms of chromium may be less mobile under some conditions. Based upon experimental BCF values for fish, chromium has a moderate potential for bioaccumulation. These fate characteristics suggest several potential exposure pathways.

Volatilization of chromate or other forms of chromium from a disposal site is not likely to represent an important exposure pathway under most conditions. Drinking water contamination resulting from the migration of chromate or other forms of chromium may occur, although chromate is considered relatively immobile in soil. Mitre (83) reported that chromium (probably total) has been found at 53 of the 546 National Priority List (NPL) sites. It was detected at 33 sites in ground water, 33 sites in surface water, and one site in air. As chromium is a naturally occurring element, this prevalence is not necessarily an indication of widespread contamination.

In addition, the presence of chromium in ground water drinking water supplies has been observed. In three national surveys of ground water supplies from 1969 to 1980, chromium was found at levels above 5 μg/L in 77 of 795 supplies sampled (9.7%). The mean of the positive values was 16 μg/L, with a maximum of 49 μg/L (1641). Again, however, it is unclear if these levels represent contamination from anthropogenic sources. It is clear, however, that chromium in some form could be and is found in ground water.

The movement of chromate in ground water or with soil particles may result in discharges to surface waters. As a result, ingestion exposures may occur through the use of surface waters as drinking water supplies, and dermal exposures may result from the recreational use of surface waters. In addition, various forms of chromium may be taken up by aquatic organisms or domestic animals. Again, environmental conditions affect the form and the extent of bioaccumulation of chromium by aquatic organisms. However, this pathway may be important in some situations.

53.2.4 Other Sources of Human Exposure

Chromium is a naturally occurring element and, as a result, there are numerous sources of exposure to chromium. Most reports of levels in the environment or in food are given as total chromium. These data are summarized briefly here.

As mentioned above, chromium was found to some extent in ground water drinking water supplies. It was also found at levels above 5 μg/L in 24 of 142 surface water supplies (16.9%). The mean concentration at the positive values was 10 μg/L, and all concentrations were less than 25 μg/L (992).

Chromium is also commonly found in air, although at low concentrations. EPA reports that data from 1977 to 1980 show a mean chromium concentration for the urban areas sampled (16 locations) of 0.0052 μg/m³ to 0.1568 μg/m³ The maximum 24 hour average concentration was 2.487 μg/m³ The mean chromium concentrations in four non-urban background areas ranged from 0.0052 μg/m³ to 0.0090 μg/m³ (1641). Concentrations of chromium near sources can be greater, and levels as high as 13.5 μg/m³ total chromium have been reported in the vicinity of a chromium pigment producer (1642).

Most foods contain chromium at levels ranging from about 0.01 to 0.5 mg/kg, but acidic foods may contain higher levels (1641). The dietary intake of chromium from typical American diets containing 43% fat was estimated to be 62 ± 28 μg/day. For diets consisting of 25% fat, the intake was estimated to be 89 ± 56 μg/day (1643). Smokers may have an additional source of chromium as tobaccos have been found to contain 0.24 to 0.63 mg/kg chromium (1252).

The above data clearly show that there are numerous sources of exposure to chromium. The exact form of chromium depends on the source and the media.

53.3 HUMAN HEALTH CONSIDERATIONS

Although chromium can exist in several valence states, the biologically significant forms of the element are the hexavalent and trivalent chromium compounds. However, due to their greatly differing abilities to penetrate cellular membranes and associated toxicity in biological systems, hexavalent (CrVI) chromium is recognized as a toxic substance while trivalent chromium (CrIII) is regarded as essential for nutrition and relatively non-toxic (1252).

Sodium chromate is a soluble (in water), hexavalent form of chromium. Other chromium compounds that are also categorized as soluble and hexavalent and therefore expected to exhibit similar toxicity, include potassium chromate, sodium or potassium dichromate and chromium trioxide (CrO_3) (1252).

53.3.1 Animal Studies

53.3.1.1 Carcinogenicity

Inconclusive findings have been reported for the carcinogenicity of hexavalent chromate in a variety of laboratory animals, tested by various routes (1252).

Levy et al. (1671) investigated the carcinogenicity of sodium chromate or sodium dichromate in 48 male and 52 female Porton-Wistar rats. Each rat received a steel pellet loaded with 2 mg of the test substance suspended in cholesterol. The pellet was implanted in the left bronchus. After 2 years, the lungs were examined. Both chromium compounds induced squamous metaplasia in the lungs of 18% (16/89) of the rats exposed to sodium chromate and 19.1% (17/89) of the rats exposed to sodium dichromate. Squamous metaplasia is regarded to be a preneoplastic lesion.

Steffee and Baetjer (1233) exposed guinea pigs by inhalation to a mixture of chromate dust, aerosols of potassium dichromate and sodium chromate, and pulverized residue dust obtained from roasted material from which soluble chromates had leached. The mixture was inhaled 4-5 hours/day, 4 days/week for the animals' life span. Pulmonary adenomas developed in 6% of the guinea pigs (vs. zero in the control group). Negative results were obtained in a separate experiment with eight rabbits exposed by inhalation to the same chromate mixture for 4-5 hours/day, 4 days/week for 50 months (1233).

Male Wistar rats were exposed in a chamber to 0, 25, 50 or 100 $\mu g/m^3$ sodium dichromate aerosol 22-23 hours/day for 18 months and observed for an additional 12 months. No clinical signs of irritation or toxicity were observed. One adenocarcinoma and 2 adenomas were present in the lungs of 19 surviving rats exposed to 100 $\mu g/m^3$ sodium dichromate. A squamous cell carcinoma in the pharynx region was also reported in the high exposure group. No lung tumors were found in the 25 or 50 $\mu g/m^3$ group (1809).

Heuper and Payne (1672) intramuscularly injected 39 Bethesda Black rats with 2 mg sodium dichromate in gelatin. Injections were administered monthly for 16 months and rats were observed for 24 months. By the 18th month, only 17 (43.6%) of the rats were alive. No tumors were observed at the injection site in any of the rats. Intrapleural injections of 2 mg sodium dichromate into 39 Bethesda Black rats once a month for 16 months gave similar results. One adenocarcinoma of the lung (0.025 incidence) was found in the chromium-treated rats. No tumors were found in control rats (1672).

The available data are inadequate to evaluate the carcinogenicity of sodium chromate. There is sufficient evidence of respiratory carcinogenicity in men occupationally exposed to chromate during chromate production but data on lung cancer risk for other chromium-associated occupations and for cancer at other sites are insufficient (1252). These studies are discussed in the Human and Epidemiologic Studies section of this chapter. IARC (1250) has determined that there is sufficient evidence for certain insoluble hexavalent chromium compounds, such as calcium chromate, sintered calcium chromate, lead chromate, strontium chromate, sintered chromium trioxide and zinc chromate, to induce cancer in rats. In that the data do not allow evaluation of the relative risk of various valence states of chromium nor soluble versus nonsoluble chromium compounds, IARC has classified all chromium compounds as Group 1 compounds (i.e., sufficient evidence of carcinogenicity to humans).

53.3.1.2 Mutagenicity

Numerous studies utilizing a variety of test systems have demonstrated that hexavalent chromium salts are mutagenic while trivalent chromium compounds are generally inactive presumably because they bind to extracellular constituents and therefore do not enter the cell (1471, 1252).

Sodium dichromate was tested in the Ames assay by Bennicelli et al. (1465) and was found to induce a strong mutagenic effect in the TA102 strain of Salmonella typhimurium. Sodium dichromate was also reported to have weak activity in strains TA1537, TA1538, and TA98 of Salmonella typhimurium (1466).

In other bacterial tests, including gene conversion in Schizosaccharomyces pombe, mitotic recombination in Saccharomyces cerevisiae, reverse mutation in Escherichia coli trp- and arg-, and the DNA repair test in Bacillus subtilis and Escherichia coli, sodium dichromate was positive (1466).

Paschin et al. (3553) observed significant increases in dominant lethal tests in which male mice were injected acutely or chronically with potassium dichromate; postmeiotic sperm appear to be the most sensitive germ cell stage. In a micronucleus test using both sexes of the same strain of mice, Paschin and Toropzev (3552) observed significant increases in micronuclei induced in bone marrow cells of mice treated in vivo with potassium dichromate.

Sarto et al. (3610) compared the clastogenicity of hexavalent and trivalent chromium compounds in human lymphocytes treated in culture. The hexavalent chromium compounds significantly increased chromosomal aberrations as well as inhibit cell division whereas observations on these effects with trivalent chromium compounds were essentially at control levels.

Chromium platers occupationally exposed to hexavalent chromium and matched controls were studied by Nagaya (1467). No differences in sister-chromatid exchange frequency was noted in lymphocytes of these two groups. The urinary chromium levels in exposed workers ranged from 2.6 μg/L to 80.3 μg/L. However, Bianchi et al. (1469) observed a significant increase in the frequency of sister-chromatid exchange in 4 rodent cell systems treated in vitro with hexavalent chromium at levels up to 10^{-3} mM.

Nishio et al. (1468) reported irreversible inhibition of DNA synthesis in cultured mouse L cells at concentrations of 10 μM hexavalent chromium and Bigaliev (1470) found chromosome aberrations in lymphocyte cultures of individuals who came in contact with chromium (potassium chromate and potassium bichromate).

Cupo et al. (1472) treated chick hepatocytes with 5 μM sodium chromate for 2 hours. DNA strand breaks, DNA interstrand cross-links, and DNA-protein cross-links were noted. After removal of the chromate, strand breaks and interstrand cross-links were completely repaired by 3 and 12 hours, respectively. A significant level of DNA-protein cross-links persisted 40 hours after chromate removal. DNA cross-links were also found in nuclei isolated from the liver and kidney of rats treated with sodium dichromate (1473).

The mutagenicity of hexavalent chromium can be decreased or eliminated by biological reducing agents such as rat liver microsomes (1252). Chemical reducing agents also appear to be effective. Gentile et al. (1471) found that chelants bind to the chromium compound and reduce or eliminate mutagenicity. Effective chelators included EDTA, salicylate and Tiron (disodium 1,2-dihydroxybenzene-3,5-disulfonate).

Thus, there is sufficient evidence that hexavalent chromium is capable of inducing DNA damage and to be mutagenic in at least three bacterial systems and mammalian cells, inducing chromosomal aberrations in a variety of mammalian cells in vitro and in vivo.

53.3.1.3 Teratogenicity, Embryotoxicity and Reproductive Effects

Little information is available on the effects of sodium chromate on reproduction. However, experimentation with other hexavalent forms of chromium have been documented in the literature. Gale (1274) intravenously administered 5, 7.5, 10 or 15 mg/kg hexavalent chromium trioxide to pregnant golden hamsters during the 8th day of gestation. Fetuses were taken on the 12th, 14th or 15th day of gestation. Lethality occurred in 75% of the dams treated with the 15 mg/kg dose and the rates of resorptions were increased for the 7.5 (29%) and 10 mg/kg (41%) groups vs. 2%

for controls. The rate of malformations also increased with dose. The incidence of cleft palate was statistically significant in all treatment groups (34% in the 5 mg/kg group, 85% in the 7.5 mg/kg group, 84% in the 10.5 mg/kg group vs. 2% in control animals). Other malformations included exencephaly (brain outside skull), rib fusion, micrognathia (unusual smallness of the jaw), ventral body wall defect, abnormal hind limbs, encephalocele (hernia of the brain), tail abnormalities, renal agenesis and hydrocephalus. In a later study with six different strains of hamsters, Gale (3234) observed a strain effect when pregnant females were exposed intravenously to 8 mg/kg of chromium trioxide on gestation day 8. The strains in which the greatest maternal toxicity was observed were also the strains in which greater fetotoxicity and teratogenicity occurred.

The embryo permeability and potential embryotoxic effects of sodium dichromate in mice were investigated by Danielsson et al. (1462). Forty-two pregnant C57BL mice were intravenously administered a single dose of sodium dichromate (hexavalent state) or chromium trichloride (trivalent state) during gestation days 8 through 18. In the sodium dichromate treated mice, animals injected on day 13 of gestation had embryonic chromate concentrations of 12% one hour after injection, while the chromium trichloride treated mice had a concentration of 0.4% at the same time period. From this point of gestation on (i.e., late gestation), both forms of chromate accumulated in the calcified areas of the fetal skeleton. The fetal concentration of both Cr III and Cr VI increased with gestational age.

53.3.1.4 Other Toxicologic Effects

53.3.1.4.1 Short-term Toxicity

Toxic effects of acute chromium (VI) exposure include skin ulcerations, rhinitis, gastritis, dyspnea, pulmonary edema and kidney damage (46). Unlike Cr (III) compounds, Cr (VI) compounds tend to cross biological membranes quite readily and are somewhat more readily absorbed from the gut or through the skin (1464). The oral LD_{50} of sodium chromate in the rat is 50 mg/kg (59). The dermal LD_{50} for sodium chromate in the rabbit is 1600 mg/kg (59).

Hughes (1474) injected a 0.08 M solution of sodium dichromate into the corneal stroma of rabbits. The reaction produced was considered severe and was graded 70 on a scale of 1 to 100. A 0.08 M solution of sodium chromate produced a similar reaction when injected into the cornea of rabbits (1474). Application of sodium chromate crystals to intact rabbit cornea for 2.5 minutes resulted in localized endothelial injury and blue stromal edema (19). Crystals of sodium dichromate produced a similar, but more severe reaction along with gross bulging of the cornea (19).

Sodium dichromate is used as an additive in mud drilling in the oil industry and resulted in a rare case of acute chromate poisoning in cattle (1773). Two hundred sixty yearling heifers were turned out into a large pasture that contained an oil drilling operation. Several days later, 10 animals were found dead. Post-mortem

examination showed gastroenteritis with a hemorrhagic abomasum and bloody ingesta in the small intestine, hemorrhages in the rectum, and congested and swollen kidneys. Histopathological examination revealed degeneration of multiple individual hepatocytes, necrosis and tubular degeneration in the kidney. Chromium levels in the kidney of two animals were 67.4 and 71.8 ppm. No additional deaths were reported after clean-up of the area.

In an inhalation study by Johansson et al. (3980), rabbits inhaled aerosols of hexavalent chromium (Na_2CrO_4) and trivalent chromium ($Cr(NO_3)_3$)at concentrations of 0.9 and 0.6 mg/m^3 of the metal, respectively, for 4-6 weeks (5 days/week and 6 h /day). The number of macrophages lavaged from the rabbits' lungs was significantly increased in animals exposed to Cr(VI) ($P = 0.05$) but not in animals exposed to Cr(III) as compared with the controls. Both Cr(III) and Cr(VI) produced morphological changes in the alveolar macrophages, but Cr(III) produced more conspicuous changes. This was unexpected since Cr(III) is considered relatively innocuous compared to Cr(VI). The most pronounced change seen with Cr(VI) was enlarged lysosomes which contained short lamellae and electron dense patchy inclusions.

Cats exposed by inhalation to 11-23 mg/m^3 hexavalent chromium (as dichromate) for 2-3 hours/day for 5 days developed bronchitis and pneumonia but no effects were observed in similarly exposed rabbits (1464).

Kidney damage is a major deleterious effect of sodium chromate in mammals (1661, 1662, 1669, 1670). Evan et al. (1661) investigated the sequence of structural changes in the kidneys of male Wister rats injected intraperitoneally with 0, 10 or 20 mg/kg sodium chromate. Kidneys were examined 1, 6, 24 and 48 hours after treatment. Electron microscopy revealed that the structural changes were confined to the microvilli of the convoluted portion of the proximal tubule and were first seen 1 hour after the 20 mg/kg dose and 6 hours after the 10 mg/kg dose. The majority of nephrons appeared to be damaged resulting in a reduction in renal blood flow or ischemia.

Kirschbaum et al. (1662) continued the investigation of the effect of sodium chromate on the kidney by studying brush border alterations of the proximal tubule following chromium administration. Female Sprague-Dawley rats were subcutaneously injected with 20 mg/kg sodium chromate and observed for 4 hours. Excretion of N-acetyl-glucosaminidase, a lysosomal enzyme widely accepted as a sensitive indicator of cell damage, was significantly increased. Urine lysozyme excretion was also markedly elevated indicating either decreased reabsorption of filtered lysozyme or release of lysozyme from renal epithelium.

An immunoassay method for measuring beta-2 microglobulin (B2-m) in the urine of rats was described by Viau et al. (3982) as a useful tool for assessing the nephrotoxicity of sodium chromate. The excretion of B2-m was compared to the excretion of the enzyme beta-N-acetyl-D-glucosaminidase (NAG), albumin, and amino acids in the rats. Female Sprague Dawley rats were given a single s.c. injection of

sodium chromate at concentrations of 5 or 10 mg/kg, while controls were given physiological saline. Both doses of sodium chromate resulted in an increased excretion of B2 m which peaked at 3 and 60 times the control level for the 5 and 10 mg/kg doses respectively. The maximum increase of NAG was reached 2 days after the administration of the 10 mg/kg dose and was 4 times the control level, but the value rapidly decreased toward the control level as the kidneys of the rats recovered from the acute injury. The 5 mg/kg dose was practically without effect on the excretion of NAG. The urinary excretion of albumin was similar in that the dose of 10 mg/kg sodium chromate induced an increased excretion of albumin with a peak (100 times the control value) on day 2. The 5 mg/kg dose was without effect. The peak of B2-m excretion was 1 day earlier than in the case of NAG and albumin, but in all these cases the injury was reversible. The targets of the sodium chromate intoxication were the proximal convoluted tubular cells (1661).

De Ruiter et al. (3981) studied the effects of E-8 M to E-3 M sodium chromate on cultured Chinese hamster kidney cells for 48 hr. Cell proliferation was inhibited significantly ($p < 0.001$) at concentrations of E-5 M to E-3 M. At these same concentrations, sodium chromate was cytotoxic, as shown by the significant increase ($p < 0.001$) in lactate dehydrogenase released by the cultured cells, and glucose consumption and lactate production were impaired.

In another experiment, male Sprague-Dawley rats were given an intraperitoneal injection of 20 or 40 mg/kg sodium dichromate while control rats were given 0.5 mL of 0.9% NaCl solution. Rats were sacrificed by decapitation 0 to 40 hours post-injection. The nuclei from the right renal cortex of the kidney, the front hepatic lobe of the liver or the whole lung were examined for DNA damage. Results indicated that rat liver cells might be more efficient at repairing hexavalent-chromium induced DNA damage than kidney or lung cells, and the lung and kidney were more sensitive than the liver to chromium-induced DNA damage (1669).

53.3.1.4.2 Chronic Toxicity

Hexavalent chromium can be tolerated by animals in low concentrations especially when administered in feed or drinking water, in which the degree of absorption is a factor. For example, dogs administered hexavalent chromium (as potassium chromate) in drinking water for 4 years at a level of 0.45 to 11.2 mg/L exhibited increased chromium concentrations in liver and spleen but no significant pathological changes (1464, 1462). A similar study in rats indicated no adverse effects with exposure to 25 ppm in drinking water for one year (1463).

Nageswara-Rao et al. (1775) studied the effects of a diet of sodium chromate-treated, parboiled rice fed to Swiss mice and chicks for one year. The chromium content of the treated rice was 0.7 ppm. No effect on food intake, growth or organ weight was observed in any of the animals and histological evaluations were normal.

Accumulation of chromium in mammalian tissues begins to occur at levels of 5 mg/L or more hexavalent chromium in drinking water (1463). Rats exposed to 4 mg/L hexavalent chromium in drinking water exhibited no adverse effects on growth rate, food intake or blood chemistry but chromium was found in tissues; even levels of 25 mg/L hexavalent chromium in the drinking water of rats for 6 months produced no histopathology (1463).

53.3.2 Human and Epidemiologic Studies

53.3.2.1 Short-term Toxicologic Effects

The lethal human dose of various forms of hexavalent chromium compounds by ingestion is estimated to be in the range of 1.5 to 16 g (1452). Hemorrhagic changes are normally seen in various organs, especially the gastrointestinal tract, in fatal poisoning cases, pathological changes in the kidneys are also observed (1452).

Ingestion of hexavalent chromium (as sodium dichromate) usually results in profuse vomiting and diarrhea with erosions, abdominal pain, bleeding and circulatory collapse. Symptoms, which may occur up to 72 hours after exposure, include thrombocytopenia with bleeding diathesis, anemia, intravascular hemolysis, acute tubular necrosis, hepatitis, seizures and other CNS disturbances (1663). Mortality usually occurs in one of two phases: early multisystem involvement may occur resulting in shock as the most prominent cause of death; if the victim survives the initial phase, hepatic and renal failure may occur and result in death (1664).

A fatal case of sodium dichromate ingestion was reported by Ellis et al. (1664). A 22-month-old boy ingested an unknown quantity of sodium dichromate solution. Vomiting was immediately induced. Fifteen minutes post-ingestion the boy was admitted to the hospital for treatment. Twelve hours post-ingestion the boy suffered cardiopulmonary arrest but was resuscitated. A generalized seizure was noted 18 hours post-ingestion. The infant died 30 minutes later. Autopsy revealed gross edema with a 2 kg weight gain over the 18 hours of hospitalization. Bilateral pleural effusions and marked pulmonary edema with severe bronchitis and acute bronchopneumonia were also present. Microscopic examination of the heart revealed wavy fibers suggestive of early hypoxic changes. The liver was congested and necrotic hepatocytes were noted. Acute tubular necrosis was noted in the kidneys. Severe submucosal edema was present in the stomach. Necrosis of the mucosa and marked edema of the submucosa were observed in duodenal and jejunal tissue. The ileum and colon had minimal mucosal necrosis and severe submucosal edema. The lumens of the duodenum, jejunum and colon were filled with unclotted blood.

Recovery following ingestion of a lethal dose of sodium dichromate was described by Walpole et al. (1663). A 24-month-old boy began to cough and vomit profusely 2-3 minutes after ingesting 50 mL of 10% sodium dichromate solution. The boy became pale, sweaty, lethargic and drowsy. He recovered soon after treatment and was discharged from the hospital on day six. Three weeks later, he began to vomit and developed symptoms of probable dysphagia (difficulty in swallowing). Further

progress was uneventful except for emotional disturbance and the onset of seizures 2 months after ingestion. Since the boy had ingested a lethal dose of sodium dichromate, Walpole speculated that the initial profuse vomiting saved the boy from lethal renal complications.

53.3.2.2 Chronic Toxicologic Effects

Chronic toxicity problems associated with chromium exposure are of concern primarily in an industrial environment. Such effects have been reviewed in detail elsewhere (1463,1252).

Hexavalent chromium causes ulceration of the skin and ulceration and perforation of the nasal septum. This is due to the reduced vascularity of the mucous membrane lining the nasal fossae which allows it to be easily destroyed. The destruction of this tissue cuts off the blood supply to the cartilage resulting in necrosis. This ulcerative process stops once it reaches the bone. At this point, healing takes place, usually with ecthymatous crust covering the mucus. The beginning of the process is characterized by sneezing and the ordinary symptoms of nasal catarrh. Pain is not significant and the only apparent inconvenience is the formation of mucous plugs in the nasal passages (1463).

A study conducted by the United States Public Health Service investigated 897 workers in seven chromate-producing plants (1673). The time each employee worked in the chromate industry was compared with the incidence of nasal septum perforation. The incidence of nasal septum perforation increased significantly as duration of employment in the chromium industry increased (see Table 53-2).

Ulceration may also occur when chromium comes in contact with the skin. These ulcerations are referred to as "chromeholes" and are usually noted at the base of the finger nails, the knuckles, the eyelids, the edges of the nostrils, the toes and occasionally the throat. The ulceration is usually slow to occur, deep and not very painful (1463).

Allergenic contact dermatitis is a major problem faced by industries using chromium. Chromium dermatitis tends to persist, and to resist therapy due to its ability to remain in the dermis of the affected areas even after exposure has been discontinued. Hexavalent chromium which gets into the skin is reduced to the trivalent form and combines with skin proteins to form complete antigens capable of causing sensitization. Milner (1791) described a worker in a printing company who was constantly exposed to chromium. Dermatitis was controlled for 7 years by antihistamines and steroids, however, symptoms began to increase in severity. The worker experienced severe discomfort due to swelling, oozing, weeping, and fissuring of the hands and wrists. A patch test to 0.25% potassium dichromate was strongly positive. Application of a 10% ascorbic acid solution to the hands hourly while at work resulted in complete elimination of the dermatitis within one month. Hexavalent chromium is reduced to the trivalent form, by ascorbic acid, which impedes passage into the skin and prevents dermatitis.

TABLE 53-2
PERFORATION OF NASAL SEPTUM IN CHROMATE WORKERS

Duration of Employment in the Chromate Industry	All Workers		
	Total Number	Workers with Perforation Number	%
Less than 6 months	41	1	2.4
6 months to 3 years	117	46	39.3
3 to 10 years	370	205	55.4
Over 10 years	369	257	69.6
TOTAL:	897	509	56.7

Source: 1673

Dust or mist containing hexavalent chromium irritates mucous membranes and causes sneezing, rhinorrhea, irritation and redness of the throat and general bronchospasm. Sensitization may develop, resulting in typical asthmatic attacks which recur on later exposure. Exposure to high concentrations may produce coughing, headache, dyspnea and substernal pain (1463).

A case of a delayed anaphylactoid reaction to sodium chromate was reported by Moller et al. (1776). A 29-year-old welder with a 10 year chromate-exposure history experienced transient skin and eye irritation after an overexposure to chromic acid mist. Twelve hours later he developed periorbital pain, swelling, and a diffuse urticarial eruption. Upon return to work 5 months later, the reaction recurred and was associated with chest tightness and dyspnea. He experienced a third episode at home following several hours of arc welding. Intradermal and prick tests to sodium chromate were negative. However, four hours after a bronchial challenge with 29 $\mu g/m^3$ sodium chromate for 25 minutes, he developed generalized urticaria, facial angioedema and bronchospasm. Blood analysis revealed a three-fold increase in plasma histamine. Skin biopsy showed a perivascular mixed cellular infiltrate with edema. Moller concluded that a delayed anaphylactoid reaction in response to inhaled metal salt had occurred, possibly via cell-mediated immunity.

Several studies suggest a correlation between cancer mortality, and industrial chromate exposure (1665, 1666, 1250). Mortality was investigated in 178 male employees and retirees from 9 chromeplating plants. All subjects had worked with chromium for at least one year during the period of January 1, 1951 through

December 31, 1981 (1665). The current air concentrations averaged 7 $\mu g/m^3$ as chromium trioxide near the chromium baths and 3 $\mu g/m^3$ in the middle of the room. However, investigations performed in the same plants prior to 1980 reported higher mean chromium trioxide concentrations, i.e., 109 $\mu g/m^3$ near the chromium baths and 35 $\mu g/m^3$ in the middle of the room (1665). A total of 15 deaths had occurred, fairly close to the expected number (15.4), however, mortalities from tumors significantly exceeded the expected number (8 vs. 4.2). Malignancies were almost entirely observed in the group of workers exposed to chromic acid in hard chromeplating plants. The incidence of death from lung cancer was significantly increased ($P = 0.03$) and a higher mortality from stomach tumors was seen in the chromeplating workers.

A retrospective study carried out by Becker et al. (1666) investigated the cancer risk of arc welders exposed to fumes containing chromium and nickel. The study consisted of 1224 male welders and 1694 male turners. The turners worked in the same environment as the welders but were not exposed to air-borne nickel and chromium. Becker noted that although not exposed to chromium, the turners were exposed to mineral cutting oils containing nitrosamines which may represent a cancer risk. The study noted 77 deaths in the welders (6.3%) and 163 deaths in the turners (9.6%). After an adjustment for age was made, a statistically significant incidence of malignant neoplasms was observed in welders exposed to nickel and chromium welding fumes for over 30 years.

Analysis of 11 cases of lung carcinoma in chromate factory workers was reported by Nishiyama et al. (1667). The average duration of exposure was 23.9 years. The age of onset ranged from 41 to 68 years. Ten of the eleven were heavy smokers; seven of the workers had perforation of the nasal septa. The primary sites of the cancers were the bronchi. A total of 9 squamous cell carcinomas and 3 small cell carcinomas were found.

53.3.3 Levels of Concern

The EPA (355) has set an ambient water quality criteria for total chromium (VI) of 0.05 mg/L. The interim MCL for chromium is 0.05 mg/L (296). The EPA has proposed that this value be changed to 0.1 mg/L (3883). EPA (992) has proposed a Lifetime Health Advisory for noncarcinogenic risks from exposure to total chromium in drinking water of 0.1 mg/L.

The WHO (666) recommends a drinking water level of 5 ug/L total chromium.

IARC (1250) lists chromium and its compounds in category 1 (sufficient evidence of human carcinogenicity) in its weight-of-evidence ranking of potential carcinogens.

The OSHA standard for chromic acid and chromates (as CrO_3) is a ceiling of 0.1 ppm (3539).

53.3.4 Hazard Assessment

Carcinogenicity findings for hexavalent chromium in a variety of laboratory animals tested by various routes have resulted in inconclusive results (1252). The data specific to sodium chromate are inadequate to evaluate its carcinogenic potential. However, sufficient evidence exists of the carcinogenicity of certain insoluble hexavalent chromium compounds. In addition, several epidemiologic studies indicate an increased risk of lung cancer among workers exposed to a mixture of chromium (VI) compounds in the chromate production industry (1665, 1666, 1250). The chromium compound(s) responsible has not been established. In that available evidence does not permit a clear delineation of the relative contribution of chromium compounds of different oxidation states or solubilities, IARC (1250) classifies all chromium compounds as Group 1 (i.e., sufficient evidence of carcinogenicity to humans).

The USEPA (667) has calculated an upper-limit incremental cancer potency factor of 41 $(mg/kg/day)^{-1}$ for chromium based on human occupational data.

Hexavalent chromium salts are mutagenic in several bacterial systems, induce chromosomal aberrations in a variety of mammalian cells and are capable of inducing DNA damage (1465, 1466, 1469, 1470, 1472).

Hexavalent chromium is also embryotoxic to mice and hamsters and induced malformations in surviving hamster fetuses, including cleft palate and skeletal defects (1274, 1462). Hexavalent chromium compounds readily cross biological membranes and can be absorbed from the gastrointestinal tract, the lungs and via the skin (1464). Toxic effects of chromium (VI) exposure include gastritis, rhinitis, dermatitis, skin ulcerations and kidney damage (1452, 46).

Dusts of hexavalent chromium compounds are severe irritants of the nasopharynx, lungs and skin and have been linked to production of ulcerated nasal mucosa, perforated nasal septa and pulmonary edema (1463).

Ingestion of toxic doses of chromium (VI) compounds usually results in vomiting, abdominal pain, bleeding and diarrhea (1663); toxic levels induce hepatic and renal failure (1664). The lethal ingested dose for humans is estimated to be in the range of 1.5 to 1.6 g. (1452).

53.4 SAMPLING AND ANALYSIS CONSIDERATIONS

Determination of sodium chromate (as chromate) concentrations in soil and water requires collection of a representative field sample and laboratory analysis for hexavalent chromium [Cr(VI)]. For the determination of trace metals, care is required to prevent losses and avoid contamination during sample collection. Samples may be collected in either glass or plastic containers; for metals, polyethylene with a polypropylene cap (no liner) is preferred. Samples should be preserved by cooling

and maintaining samples at 4°C until analysis. Samples should be analyzed as soon as possible after collection; maximum holding time is 24 hours. In addition to the targeted samples, quality control samples such as field blanks, duplicates, and spiked matrices may be specified in the recommended methods.

EPA-approved procedures for the analysis of hexavalent chromium in aqueous samples include Methods 218.4 and 218.5 (1420), 7195, 7196, and 7197 (65) and 303B (1422). Methods 218.4, 7197, and 303B are based on chelation of hexavalent chromium with ammonium pyrrolidine dithiocarbamate (APDC) and extraction with methyl isobutyl ketone (MIBK); the sample extract is aspirated into the flame of an atomic absorption spectrophotometer for determination of a hexavalent chromium concentration. Hexavalent chromium may also be chelated with pyrrolidine dithiocarbamic acid in chloroform; a colorimetric procedure using diphenylcarbazide may also be used to determine the hexavalent chromium concentration. Methods 218.5 and 7195 are based on the separation of hexavalent chromium from the sample by coprecipitation of lead chromate with lead sulfate in a solution of acetic acid. After separation, the supernate is drawn off and the Cr(VI) precipitate is reduced and resolubilized in nitric acid. The trivalent chromium is quantified by furnace (Methods 218.5 and 7195) or flame (Method 7195) atomic absorption. In addition, hexavalent chromium may be determined colorimetrically by reaction with diphenylcarbazide in acid solution using Method 7196; a red-violet color is produced whose absorbance may be measured spectrophotometrically. Molybdenum, vanadium, and mercury may interfer in this analysis if the chromium concentration is low.

The EPA procedures recommended for determination of hexavalent chromium concentrations in aqueous samples may also be applicable to the determination of hexavalent chromium concentrations in soil and waste samples. These procedures differ primarily in the preparation of the sample for analysis; hexavalent chromium must be solubilized and separated from the sample matrix prior to analysis.

Hexavalent chromium in environmental systems is generally partially converted to trivalent chromium through reduction; there are several EPA-approved procedures for the determination of "total chromium" in both aqueous and non-aqueous samples. These methods include Methods 218.1, 218.2, and 218.3 (1420), 7190 and 7191 (63) and 303A, 303B, and 304 (1422). Samples for determination of total chromium may also be collected in either glass or plastic containers. Sample preservation involves adding concentrated nitric acid in the field until the pH of the sample is less than 2; maximum holding time is six months.

Typical detection limits for hexavalent chromium that can be obtained in wastewaters are shown below; detection limits were not indicated for nonaqueous samples. The actual detection limit achieved in a given analysis will vary with instrument sensitivity and matrix effects.

Aqueous Detection Limit
10 µg/L (Method 218.4)
5 µg/L (Method 218.5)
5 µg/L (Method 7195)
500 µg/L (Method 7196)
1 µg/L (Method 7197)

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Note: The nonsequential numbers of the references reflect the order of references as they appear in the master bibliography.

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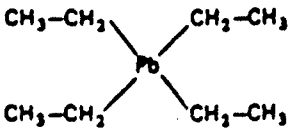
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COMMON SYNONYMS:	CAS REG.NO.: FORMULA:	AIR W/V CONVERSION FACTOR at 25°C
TEL Tetraethyl lead Tetraethyl plumbane	78-00-2 $C_8H_{20}Pb$ NIOSH NO: TP4550000 STRUCTURE: 	13.22 mg/m³ ≈ 1 ppm; 0.075 ppm ≈ 1 mg/m³ MOLECULAR WEIGHT: 322.45

REACTIVITY	Various sources indicate that reaction of tetraethyl lead with strong oxidizing agents such as potassium permanganate or sulfuryl chloride may cause a fire or explosion and that the compound is also incompatible with concentrated acids. Exposure to sunlight may cause decomposition to tri-, di-, and mono-ethyl lead compounds. Decomposition may also occur due to heating (with attendant pressure rise in closed containers) and reaction with rust and certain other metals. Chemical compatibility charts suggest other general incompatibilities with organic peroxides or hydroperoxides, epoxides, explosives, and polymerizable compounds. Stable below 230°F; at higher temperatures, may detonate or explode when confined (38, 54, 60, 511, 512).

PHYSICO-CHEMICAL DATA	• Physical State: Liquid, oily (at 20°C)	(23)
	• Color: Colorless (may be dyed red, orange, or blue)	(23)
	• Odor: Sweet	(60)
	• Odor Threshold: No data	
	• Density: 1.6530 g/mL (at 20°C)	(14)
	• Freeze/Melt Point: -137.00°C	(14)
	• Boiling Point: 152°C at 291 mm	(14)
	• Flash Point: 85°C (open cup); 93.3°C (closed cup)	(38,60,506)
	• Flammable Limits: 1.80 to ? % by volume; max is unknown	(506)
	• Autoignition Temp.: Decomposes first	(23,38,60)
	• Vapor Pressure: 1.50E-01 mm Hg (at 20°C)	(67)
	• Satd. Conc. in Air: 2.6600E+03 mg/m³ (at 20°C)	(1219)

PHYSICO-CHEMICAL DATA (Cont.)	• Solubility in Water: Insoluble (23) • Viscosity: 0.864 cp (at 20°C) (21) • Surface Tension: 2.8500E+01 dyne/cm (at 20°C) (60) • Log (Octanol-Water Partition Coeff.): No data • Soil Adsorp. Coeff.: 2.29E+04 (1716) • Henry's Law Const.: 9.00E-01 atm · m³/mol (at 20°C) (1715) • Bioconc. Factor: 1.20E+02 (mussel); 6.5E+02 (shrimp) 1.81E+04 (oysters) (3761)

PERSISTENCE IN THE SOIL-WATER SYSTEM	Tetraethyl lead is expected to be relatively immobile and non-persistent in soil due to degradation, sorption, and volatilization. Typical half-lives in water are on the order of one week, and degradation has generally been found to be enhanced in sunlight.

PATHWAYS OF EXPOSURE	The primary exposure pathway of concern from soil/ground-water systems is the migration of tetraethyl lead to groundwater drinking water supplies, although it is relatively immobile and may degrade under some conditions. Exposures through inhalation may also be important in some situations.

HEALTH HAZARD DATA	Signs and Symptoms of Short-term Human Exposure: (38, 51) Mild symptoms of tetraethyl lead intoxication include headache, anxiety, insomnia, nausea, appetite loss, low body temperature, slow heart beat and tremor. Skin contact may cause itching, burning and redness. The liquid and vapor may be irritating to the eyes. Acute Toxicity Studies: INHALATION: LC_{50} 850 mg/m³ · 1 hr Rat ORAL: LD_{50} 12.3 mg/kg Rat Long-Term Effects: Neurotoxicity Pregnancy/Neonate Data: Not teratogenic in animals; fetotoxic at doses producing maternal toxicity Genotoxicity Data: Limited data negative Carcinogenicity Classification: IARC - Group 3 (not classifiable as to its carcinogenicity to humans) NTP - None assigned EPA - Group B2 (probable human carcinogen; sufficient evidence in animals and inadequate evidence in humans)
HANDLING PRECAUTIONS	Handle only with adequate ventilation • Vapor concentrations of 0.075-0.75 mg/m³: any supplied-air respirator or selfcontained breathing apparatus • 0.75-3.75 mg/m³: any supplied-air respirator or self-contained breathing apparatus with full facepiece • 3.75-40 mg/m³: a type-C supplied-air respirator operated in pressure demand or other positive pressure or continuous-flow mode • Chemical goggles if there is probability of eye contact • Protective clothing to prevent skin contact.

ENVIRONMENTAL AND OCCUPATIONAL STANDARDS AND CRITERIA

AIR EXPOSURE LIMITS:

Standards

- OSHA TWA (8-hr): 0.075 mg/m³ (as Pb) (skin)
- AFOSH PEL (8-hr TWA): 0.075 mg/m³ (as Pb) (skin); STEL (15-min): 0.225 mg/m³

Criteria

- NIOSH IDLH (30-min): 40 mg/m³ (as Pb)
- NIOSH REL: no data
- ACGIH TLV® (8-hr TWA): 0.1 mg/m³ (as Pb) (skin)

WATER EXPOSURE LIMITS:

Drinking Water Standards (296,991)
The national interim drinking water regulation for lead is 50 µg/L at the tap. The proposed MCL at the source is 5 µg/L, and the proposed MCLG at the source is 0. This MCL applies to community water systems which serve a population of 10,000 people or more and which add a disinfectant as part of their treatment process.

EPA Health Advisories and Cancer Risk Levels
None established

WHO Drinking Water Guideline (666)
A health-based guideline for drinking water of 0.05 mg/L is recommended for lead. A daily per capita consumption of two liters of water was assumed.

EPA Ambient Water Quality Criteria

- Human Health (3770)
  - The ambient water quality criterion for lead is recommended to be identical to the existing drinking water standard which is 0.05 mg/L.

- Aquatic Life (3770)
  - Freshwater species
    Freshwater aquatic organisms and their uses should not be affected unacceptably if the 4-day average concentration (in µg/L) of lead does not exceed the numerical value given by e(1.273[ln(hardness)]-4.705) more than once every 3 years on the average and if the 1-hour average concentration (in µg/L) does not exceed the numerical value given by e(1.273[ln(hardness)]-4.460) more than once every 3 years on the average.

ENVIRONMENTAL AND OCCUPATIONAL STANDARDS AND CRITERIA (Cont.)

- Saltwater species
  Saltwater aquatic organisms and their uses should not be affected unacceptably if the 4-day average concentration of lead does not exceed 5.6 µg/L more than once every 3 years on the average and if the 1-hour average concentration does not exceed 140 µg/L more than once every 3 years on the average.

REFERENCE DOSES:
No reference dose available.

REGULATORY STATUS (as of 01-MAR-89)

Promulgated Regulations
- Federal Programs

Clean Water Act (CWA)
Tetraethyl lead is designated a hazardous substance (347). Lead and lead compounds are listed as toxic pollutants, subject to general pretreatment regulations for new and existing sources, and effluent standards and guidelines (351, 3763). Limitations vary depending on the type of plant and industry.

Safe Drinking Water Act (SDWA)
Lead is on the list of 83 contaminants required to be regulated under the SDWA of 1974 as amended in 1986 (3781). Under the National Primary Drinking Water Regulations, the maximum contaminant level (MCL) for lead at the water tap is 0.05 mg/L. This MCL applies to community water systems which serve a population of 10,000 people or more and which add a disinfectant as part of their treatment process (3800). In states with an approved Underground Injection Control program, a permit is required for the injection of tetraethyl lead-containing wastes designated as hazardous under RCRA (295).

Resource Conservation and Recovery Act (RCRA)
Tetraethyl lead is identified as an acute hazardous waste (P110) and listed as a hazardous waste constituent (3783, 3784). Lead compounds are also listed as hazardous waste constituents (3783). Waste streams from the following industries contain lead and are listed as specific sources of hazardous waste: iron and steel, secondary lead, petroleum refining and explosives, (3774, 3765). Solid wastes are listed as hazardous in that they exhibit the characteristic defined as EP toxicity when the TCLP extract concentration is equal to or greater than 5.0 mg/L lead (968). Used oil that is burned for energy recovery may not contain greater than 100 ppm lead (1768). Effective July 8, 1987, land disposal of untreated liquid hazardous wastes, including free liquids associated with any solid or sludge-containing lead and/or its compounds at concentrations greater than or equal to 500 mg/L is prohibited. Effective August 8, 1988, the underground injection into deep wells of these wastes is prohibited. Certain variances exist until May, 1990 for some wastewaters and soils for which Best Demonstrated Available Technology (BDAT) treatment standards have not been promulgated by EPA (3786). Lead is included on EPA's ground-water monitoring list. EPA requires that all hazardous waste treatment, storage, and disposal facilities monitor their ground-water for chemicals on this list: when suspected contamination is first detected and annually thereafter (3775). For ground-water protection, the maximum concentration of lead-containing hazardous waste allowed in ground-water is 0.05 mg/L (989).

Comprehensive Environmental Response Compensation and Liability Act (CERCLA)
Tetraethyl lead is designated a hazardous substance under CERCLA. It has a reportable quantity (RQ) limit of 4.54 kg. Reportable quantities have also been issued for RCRA hazardous waste streams containing tetraethyl lead but these depend upon the concentrations of the chemicals in the waste stream (3766). Tetraethyl lead is designated an extremely hazardous substance under SARA Title III Section 302. Any facility at which tetraethyl lead is present in excess of its threshold planning quantity (TPQ) of 100 pounds must notify state and local emergency planning officials. If tetraethyl lead is released from the facility in excess of its reportable quantity (RQ), local emergency planning officials must be notified (3766). Under SARA Title III Section 313, manufacturers, processors, importers, or users of lead compounds must report annually to EPA and state officials their releases of these chemicals to the environment (3787).

Clean Air Act (CAA)
The national primary and secondary ambient air quality standards for lead and its compounds are 1.5 mg/m^3, maximum arithmetic mean averaged over a calendar quarter (1405). As of January 1, 1986, it is prohibited to produce or import leaded gasoline with a lead content in excess of 0.10 g/gallon (1567).

Marine Protection Research and Sanctuaries Act (MPRSA)
Ocean dumping of known or suspected carcinogens, mutagens or teratogens is prohibited except when they are present as trace contaminants. Permit applicants are exempt from these regulations if they can demonstrate that such chemical constituents are non-toxic and non-bioaccumulative in the marine environment or are rapidly rendered harmless by physical, chemical or biological processes in the sea (309).

Occupational Safety and Health Act (OSHA)
Employee exposure to tetraethyl lead (as Pb) shall not exceed an 8-hour time-weighted average (TWA) of 0.075 mg/m³. Employee skin exposure shall be prevented/reduced through the use of protective clothing and practices (3539).

Hazardous Materials Transportation Act (HMTA)
The Department of Transportation has designated tetraethyl lead as a hazardous material with a reportable quantity of 4.54 kg, subject to requirements for packaging, labeling and transportation (3180).

Food, Drug and Cosmetic Act (FDCA)
The level for lead in bottled drinking water is 0.05 mg/L. This level is identical to the maximum contaminant level (MCL) given under the Safe Drinking Water Act (365).

Consumer Product Safety Act (CPSA)
No statement for tetraethyl lead from the CPSA.

- State Water Programs

ALL STATES
All states have adopted EPA Ambient Water Quality Criteria and NPDWRs (see Water Exposure Limits section) as their promulgated state regulations, either by narrative reference or by relisting the specific numeric criteria. These states have promulgated additional or more stringent criteria:

ALABAMA
Alabama has an MCL of 0.02 mg/L for lead in drinking water (3015).

ARIZONA
Arizona has an MCL of 0.1 mg/L for lead in private agricultural and semi-public water systems (981).

CALIFORNIA
California has some additional surface water quality standards for lead:

32 µg/L - Ocean Plan waters,
3.2 µg/L - Region 2 freshwaters,
5.6 µg/L - Region 2 marine and municipal waters,
5 mg/L - Region 2 and 3 agricultural waters,
30 µg/L - Region 3 freshwaters,
10 µg/L - Region 3 marine waters (3097).

FLORIDA
Florida has an additional surface water quality criterion of 30 µg/L for Class I and III waters (3220).

ILLINOIS
Illinois' general use water quality standard for lead is dependent on the hardness of the water, and is calculated with a specified formula, e(1.273[ln(hardness)]-1.460) (3321).

IOWA
Iowa has an additional surface water quality criterion of 0.1 mg/L for Class B fish and wildlife waters (3327).

KANSAS
Kansas has a quantification limit of 1 µg/L and an action level of 50 µg/L for lead in ground-water (3213).

NEBRASKA
Nebraska's acute and chronic toxicity surface water quality criteria levels for lead are dependent on the hardness of the water and are calculated on an individual basis using a state-specified formula. The criteria are for the protection of aquatic life (3719).

NEW YORK
New York has quality standards for lead: 25 µg/L for public water supply ground-waters, 8.6 µg/L for SA, SB, and SC marine waters, and 220 µg/L for SD marine waters (3500).

NORTH CAROLINA
North Carolina has a surface water quality criterion of 25 µg/L for lead in fresh and tidal salt waters (3681).

OHIO
Ohio has a surface water quality criterion of 30 µg/L for lead in all aquatic life habitat waters (3533).

OKLAHOMA
Oklahoma has a water quality criterion of 0.1 mg/L for lead in surface waters (3534).

RHODE ISLAND
Rhode Island sets surface water quality criteria for lead in Sea Water Class SB at 220 µg/L upper value and 8.6 µg/L secondary upper limit (3827).

SOUTH DAKOTA
South Dakota has a water quality standard of 0.02 mg/L for ground-water (3671).

TEXAS
Fresh water acute and chronic surface water quality criteria for lead in Texas waters is dependent on the hardness of the water and calculated on an individual basis using a specified formula. Marine water acute and chronic criteria are set at 140 and 5.6 µg/L respectively. These criteria are for the protection of aquatic life (3112).

UTAH
Utah has a surface water criterion of 0.3 mg/L for lead in Domestic Class IA and IB waters and 0.1 mg/L for Class 4 agricultural use waters (3827).

VERMONT
Vermont has a preventive action limit of 10 µg/L and an enforcement standard of 20 µg/L for lead in ground-water (3682).

VIRGINIA
Virginia has a water quality chronic criterion of 5.6 µg/L for lead in surface waters for the protection of aquatic life (3827).

WISCONSIN
Wisconsin has a preventive action limit of 5 µg/L and an enforcement standard of 50 µg/L for lead in ground-water (3840).

WYOMING
Wyoming has the following ground-water quality standards: 0.1 mg/L for Class III Livestock waters, 5.0 mg/L for Class II Agriculture waters, and 0.05 mg/L for Class I Domestic waters (3852).

Proposed Regulations

- Federal Programs

Safe Drinking Water Act (SDWA)
EPA has proposed a maximum contaminant level goal (MCLG) of zero and a maximum contaminant level (MCL) of 0.005 mg/L for lead at the water source, as part of the National Primary Drinking Water Regulations. Final promulgation is expected in September, 1989 (992).

Resource Conservation and Recovery Act (RCRA)
EPA has proposed listing as hazardous, mixtures of acutely toxic wastes, such as tetraethyl lead (1396). EPA has proposed listing wastewater treatment sludges from the sodium-lead alloy alkyl lead process and washwater from the formulation of mixed alkyl leads as specific sources of tetraethyl lead-containing hazardous waste (1397).

- State Water Programs

MOST STATES

Most states are in the process of revising their water programs and proposing changes to their regulations which will EPA's changes when they become final. Contact with state officers is advised. Changes are projected for 1989-90 (3683).

IOWA

Iowa has proposed additional acute and chronic toxicity water quality criteria for lead in Class B surface waters. Chronic toxicity values range from 3-80 µg/L, acute toxicity values from 80-750 µg/L. These criteria are for the protection of aquatic life (3326).

MINNESOTA

Minnesota has proposed a Recommended Allowable Limit (RAL) of 20 µg/L for lead in drinking water (3451). Minnesota has also proposed a Sensitive Acute Limit (SAL) for lead of 148.08 µg/L for surface waters, and chronic criteria of 4.42 µg/L for designated ground-waters and 74.05 for designated surface waters. These criteria are for the protection of human health (3452).

EEC Directives

Directive on Drinking Water (533)

The mandatory values for lead in surface water treatment categories A1, A2 or A3 are 0.05 mg/L. There are no guideline values.

Directive Relating to the Quality of Water for Human Consumption (540)

The maximum admissible concentration for lead is 50 µg/L in running water. Where lead pipes are present, the lead content should not exceed 50 µg/L in a sample taken after flushing. If the sample is taken either directly or after flushing and the lead content either frequently or to an appreciable extent exceeds 100 µg/L, suitable measures must be taken to reduce the exposure to lead.

Directive on Ground-Water (538)

Direct and indirect discharge of lead into ground-water shall be subject to prior review so as to limit such discharges.

Directive on Bathing Water Quality (534)

When inspection of a bathing area shows that heavy metals, pesticides or cyanides may be present, concentrations should be checked by competent authorities.

Directive on the Quality Required of Shellfish Waters (537)
The mandatory specifications for lead specify that the concentration of each substance in the shellfish water or in shellfish flesh must not reach or exceed a level which has harmful effects on the shellfish and larvae. The synergistic effects of other metals must be taken into consideration. The guideline specifications state that the concentration of lead in shellfish flesh must be so limited that it contributes to the high quality of shellfish product.

Directive on the Discharge of Dangerous Substances (535)
Lead cannot be discharged into inland surface waters, territorial waters or internal coastal waters without prior authorization from member countries which issue emission standards. A system of zero-emission applies to discharge of these substances into ground-water.

Directive on Marketing and Use of Dangerous Substances (541)
Tetraethyl lead may not be used in ornamental objects intended to produce light or color effects by means of different phases.

Directive on Toxic and Dangerous Wastes (542)
Any installation, establishment, or undertaking which produces, holds and/or disposes of certain toxic and dangerous wastes including phenols and phenol compounds; organic-halogen compounds; chrome compounds; lead compounds; cyanides; ethers and aromatic polycyclic compounds (with carcinogenic effects) shall keep a record of the quantity, nature, physical and chemical characteristics and origin of such waste, and of the methods and sites used for disposing of such waste.

Directive on the Classification, Packaging and Labeling of Dangerous Substances (787)
Tetraethyl lead is classified as a toxic substance and is subject to packaging and labeling regulations.

Directive on Transfrontier Shipment of Hazardous Waste (1433)
When the holder of a hazardous waste such as lead intends to ship it to another member state, authorities of the member states concerned must be provided with information on the source and composition of the waste, measures to be taken to ensure safe transport, insurance against damage and the existence of a contractual agreement with the consignee of the waste. All transfrontier shipments must be properly packed and labeled and must be accompanied by instructions to be followed in the event of danger or accident.

Directive on Paints, Varnishes, Printing Inks, Adhesives and Similar Products (1334)
Lead alkyls are classified as toxic substances when present in concentrations greater than 0.1% and as harmful substances when present in concentrations ranging from 0.05 to 0.1%. Other lead compounds are classified as harmful when present at concentrations greater than or equal to 1.0%.

Directive on the Lead Content of Petrol (1430)
The maximum permitted lead content of leaded petrol is 0.15 g/L and not more than 0.40 g/L. As of October 1, 1989, benzene content of leaded petrol and of unleaded petrol shall not exceed 5.0% by volume. Until April 1, 1990, unleaded petrol may contain up to 0.020 g/L of lead compounds.

Directive on a Limit Value for Lead in the Air (1429)
The limit value for the concentration of lead in air is 2 μg/m expressed as an annual mean concentration.

Directive on Major Accident Hazards of Certain Industrial Activities (1794)
Tetraethyl lead manufacturers are required to notify competent authorities if it is stored or processed in quantities in excess of 50 tons. If a major accident occurs, authorities must be provided with the circumstances of the accident, substances involved, emergency measures taken, and the data available for assessing the effects on man and the environment.

Directive on the Approximation of the Laws, Regulations and Administrative Provisions Relating to the Classification, Packaging and Labeling of Dangerous Prepar..ions (3991)
The labels on packages containing preparations classified as very toxic, toxic or corrosive must bear the safety advise S1/S2 and S46 in addition to the specific safety advice. If it is physically impossible to give such information, the package must be accompanied by precise and easily understood instructions.Paints and varnishes containing lead quantities exceeding 0.25% as weight of metal and less than 125 milliiitres; and glues containing cyanocrylates must contain labels indicated in Annex II of this directive.

EEC Directives - Proposed
Proposal for a Council Directive on the Dumping of Waste at Sea (1793)
EEC has proposed that the dumping of lead compounds at sea be forbidden without prior issue of a special permit.

54.1 MAJOR USES

Tetraethyl lead (TEL) is the primary component of formulated anti-knock mixtures for gasoline. Anti-knock agents prevent preignition in internal combustion engines. U.S. consumption of TEL reached a peak of 312 million kg in 1970, but has declined significantly since the Environmental Protection Agency (EPA) issued regulations requiring a gradual reduction in the lead content of gasoline. The EPA estimated that 51.8 million kg of lead were used in 1983. This is equivalent to 13 million gallons of TEL assuming that 3 ml of TEL provides 3.17 g of elemental lead (1409). TEL was also used as an intermediate in the production of organomercury fungicides, but the agricultural use of these compounds is no longer permitted in the U.S. (21, 1252).

54.2 ENVIRONMENTAL FATE AND EXPOSURE PATHWAYS

54.2.1 Transport in the Soil/Ground-water Systems

54.2.1.1 Overview

Tetraethyl lead is expected to be relatively immobile at low concentrations (dissolved in water). Bulk quantities of the liquid chemical (e.g., from a spill of the pure substance, a gasoline additive that contains it, or leaded gasoline) could be transported down through the unsaturated zone. However, as described later in this section, TEL is volatile and susceptible to a number of degradation processes (photolysis, hydrolysis, oxidation).

Environmental transport pathways for TEL can generally be assessed by using an equilibrium partitioning model, as shown in Table 54-1. These calculations predict the partitioning of low soil concentrations of TEL among soil particles, soil water, and soil air. The estimates for the unsaturated topsoil model show that, whereas almost all of the chemical (97.5%) is sorbed to the soil, a small portion (2.5%) is in the soil air; thus, it is available to diffuse through the soil-air pores to the soil surface. Migration of TEL by bulk transport (percolating water) or aqueous phase diffusion or dispersion is expected to be insignificant, because such a small fraction partitions to the soil water. In saturated, deep soils (containing no air and negligible soil organic carbon) a much greater fraction is in the mobile ground-water phase (1%), but still a very small amount compared with that sorbed to the soil.

TEL has been used in large quantities as a gasoline octane enhancer for about 60 years. However, its use is decreasing, because it cannot be used in most new cars as it poisons the catalyst used in catalytic converters. Its use in all motor fuels in the U.S. is being phased out by law.

TABLE 54-1
EQUILIBRIUM PARTITIONING CALCULATIONS FOR
TETRAETHYL LEAD IN MODEL ENVIRONMENTS[a]

Soil Environment	Estimated Percent of Total Mass of Chemical in Each Compartment		
	Soil	Soil-Water	Soil-Air
Unsaturated topsoil at 25°C[b,c]	97.5	0.022	2.5
Saturated deep soil[d]	99.0	1.0	-

a) Calculations based on Mackay's equilibrium partitioning model (34, 35, 36); see Introduction in Volume 1 for description of model and environmental conditions chosen to represent an unsaturated topsoil and saturated deep soil. Calculated percentages should be considered as rough estimates and used only for general guidance.
b) Utilized estimated soil sorption coefficient (1716): K_{oc} = 22,900.
c) Henry's law constant taken as 0.90 atm · m³/mol at 25°C (estimated using data from 1715).
d) Used sorption coefficient $K_p = 0.001\ K_{oc}$

54.2.1.2 Sorption on Soils

There appear to be few, if any, studies on the soil sorption behavior of TEL. The susceptibility of TEL to degradation by light and its high volatility complicate the assessment of its leaching potential.

No values for the equilibrium soil sorption constant, K_{oc}, for TEL were found in the literature. An average value of 22,900 has been estimated using four correlation equations and the solubility data of Feldhake and Stevens (1715). This value indicates that TEL sorbs strongly to topsoils (containing >0.1% organic carbon), i.e., a very large percentage of the chemical will be sorbed to soil, although some leaching is still possible. As with all neutral organic chemicals, the extent of soil sorption is directly proportional to the soil organic carbon content. For low organic carbon soils (e.g., clays), the extent of sorption may also depend on other properties of the soil such as surface area, cation exchange capacity, and degree of hydration.

54.2.1.3 Volatilization from Soils

TEL has a relatively high vapor pressure, which has been given as a function of temperature by Feldhake and Stevens (1715) based on the data of Buckner and Norrish (1717) as log P = 9.34286 - 2908.43/T, where P is the vapor pressure in torr, and T is the absolute temperature (°C + 273.16). This equation indicates a vapor pressure of 0.26 torr at 20°C, but a slightly lower value of 0.15 torr has also been given (67). These values together with low aqueous solubility of TEL result in a high volatility (0.90 atm · m^3/mol at 25°C based on the solubility and vapor pressure data in Reference 1715). Therefore, volatilization from soils should be an important transport pathway, if water is present, despite the tendency of TEL to sorb strongly.

54.2.2 Transformation Processes in Soil/Ground-water Systems

TEL is susceptible to a number of degradation processes including hydrolysis, photolysis, and oxidation; thus, it is not persistent in the environment.

The half-life for aqueous hydrolysis of TEL in water at pH 7 and 40°C was reported as eight days, with $(C_2H_5)_3PbOH$ being the hydrolysis product (1718). Triethyl lead hydroxide, which is soluble in water, ionizes to $(C_2H_5)_3Pb^+$.

The rate of TEL degradation in sea water and fresh water was investigated by Grove (1720) who determined a minimum half-life for the dissolved compound by measuring its concentration and those of its degradation products over time in stirred, open tanks. The minimum half-life was 12 hr in sea water and 2 days in fresh water. Using completely filled syringes of fresh water, which had not been deaerated, a half-life of about 7 days resulted. Diffused daylight did not appear to accelerate the rate of decomposition. Other studies (1721, 1722) have shown accelerated degradation of TEL in sunlight using a liter of treated ("permuted") water to which 165 mg of TEL had been added (well above the solubility limit). Charlou et al. (1721) found about 1, 20, and 97 to 100% degradation after 4 hr for samples kept in darkness, exposed to sunlight, and irradiated with UV light, respectively. The values correspond to a half-life of approximately 11.5 days for the sample kept in darkness, but only 1.5 days for the one exposed to sunlight.

Jarvie et al. (1722) found TEL in a distilled water solution to be much more stable in the dark, with only 2% of an initial 12-15E-05 M "solution" degraded after 77 days, whereas in sunlight 99% degraded after 15 days. The decomposition in darkness was found to be catalyzed by Cu^{+2} and Fe^{+3} ions; the adsorption of TEL from solution onto silica also accelerated the degradation, with 97% reacting in about 1 month.

The degradation of TEL is believed to proceed through successive dealkylations: Et_4Pb to Et_3Pb^+ to Et_2Pb^{+2} to Pb^{+2} (1719, 1722, 1723). It has also been suggested that lead alkyl ions and inorganic lead may undergo biological alkylation (1723, 1570). However, its significance in natural environments has been doubted (1722, 1723), and other work has indicated an absence of biological methylation (1724).

5423 Primary Routes of Exposure from Soil/Ground-water Systems

The above discussion of fate pathways suggests that the mobility and exposure to TEL depend on environmental conditions. This compound is considered to have a moderate volatility and to be moderately to strongly sorbed to soils. These fate characteristics suggest some possible exposure pathways.

Volatilization of TEL from a disposal site presents a potential pathway of exposure; however, the adsorption of this compound to soil may limit this occurrence as shown in Table 54-1. Drinking water contamination resulting from the migration of TEL may occur, although TEL is considered relatively immobile in soil. Mitre (83) reported that lead was one of the most commonly detected contaminants both in ground-water and surface water at National Priority List (NPL) sites. Most analyses, however, are conducted for total lead and are probably not indicative of the presence of TEL. Little information appears to be available on the presence of TEL in surface water or ground-water (1738).

The movement of TEL in ground-water or with soil particles may result in discharges to surface waters. As a result, exposure by ingestion may occur through the use of surface waters as drinking water, and dermal exposures may result from the recreational use of surface waters. In addition, TEL may be taken up by aquatic organisms or domestic animals. The extent to which these exposure pathways are important depends upon the importance of transport pathways (volatilization and adsorption to sediment) and also on the transformation of TEL in surface water. Because TEL has not been commonly reported in surface waters (1738), although analyses have been limited, the associated exposure pathways may not be as important for TEL as direct exposure through contaminated ground-water or air releases.

5424 Other Sources of Human Exposure

The use of TEL as an antiknock additive in gasoline has lead to the presence of this compound in the atmosphere, largely as a result of losses in filling, transport, and storage. As a result, concentrations are higher in such locations as parking garages and gas stations. For example, a concentration of 2000 ng/m^3 of TEL was reported in the air at the exit of a parking garage (1735). Concentrations of organolead compounds in six U.S. cities ranged from <100 to 800 ng(Pb)/m^3 of air. The ratio between tetraalkyl lead and particulate lead in air in urban areas ranges from about 0.05 to 0.1 and 1 to 110 ng/m^3 in suburban areas (1737).

As mentioned above, there is little information specifically on the presence of TEL in water, particularly drinking water supplies. TEL compounds have been found in fish. Chau et al. (1739) reported levels of TEL ranging from 0.3 to 9.3 ng/g wet weight in a variety of species of fish from Ontario, Canada.

54.3 HUMAN HEALTH CONSIDERATIONS

54.3.1 Animal Studies

54.3.1.1 Carcinogenicity

Only one study was found on the carcinogenicity of tetraethyl lead in laboratory animals. Epstein and Mantel (1253) injected male and female random-bred Swiss mice (ICR/Ha) subcutaneously with tetraethyl lead dissolved in tricaprylin. The control (124 mice) group received the vehicle alone. There were three treated groups that were treated as follows and killed 49 to 51 weeks after treatment: (1) 69 mice received one injection of 2.0 mg of tetraethyl lead on day 1 after birth; (2) 92 mice received 0.2 mg on days 1 and 7, and 0.4 mg on days 14 and 21; (3) 109 mice received 0.1 mg on days 1 and 7, and 0.2 mg of days 14 and 21. Mortality was very high. Survival was very low except in mice receiving 0.1 mg followed by 0.2 mg; lymphomas were induced in the females with an incidence of 5/41 (12%; statistically significant) at 36 weeks. No other significant neoplastic lesions were reported.

IARC (3838) concluded that there in inadequate evidence for carcinogenicity of organolead compounds (includes TEL) in animals and classifies them as a Group 3 carcinogens.

54.3.1.2 Mutagenicity

Tetraethyl lead was negative in all 4 Salmonella typhimurium strains tested with or without metabolic activation (3469). Negative findings were reported in a dominant lethal study conducted in mice (1258).

54.3.1.3 Teratogenicity, Embryotoxicity and Reproductive Effects

Tetraethyl lead is not teratogenic to either rats or mice. McClain and Becker (1259) administered oral doses of 7.5, 15 or, 30 mg/kg to rats as 3 divided doses during early or late organogenesis (days 9, 10 and 11, or 12, 13, and 14). There was 100% maternal mortality in the 30-mg/kg groups. In the remaining treatment groups, there were increased incidences of resorptions and incomplete ossification, but these effects were considered to be due to the maternal toxicity of TEL rather than to a direct effect on the fetus.

Kennedy et al. (1260) administered 0.01, 0.1, 1, or 10 mg/kg of TEL by gavage to mice and rats daily during organogenesis. Treatment with 10 mg/kg was discontinued in both species after 3 doses, because of its toxic effect; the number of pregnancies were sharply reduced in these groups. An increase in fetal resorption and growth retardation occurred in both species at the 1-mg/kg dose. Three fetuses from one litter in the group of mice receiving 0.1 mg/kg displayed torsion of the rear limbs.

Administration of TEL to 5-day-old chick embryos resulted in 100% mortality by the 11th day. When TEL was given on the 8th day, mortality was 47% by day 11.

All chicks died on the 20th day, after the opening of the egg, due to the inability to breathe. The neuromuscular systems were found to be atrophied. The administered dose was not reported (1261).

54.3.1.4 Other Toxicologic Effects

54.3.1.4.1 Short-term Toxicity

Systemic organolead poisoning can result from inhalation of the vapor or ingestion. Because of their high degree of lipid solubility, organolead compounds such as TEL are also absorbed through the skin (17, 1255). The toxicity of TEL is believed to be due to its metabolic conversion to triethyl and inorganic lead (3145 as cited by 3632).

TEL is readily absorbed from the gastrointestinal tract (3340), and it is rapidly metabolized to triethyl lead by hepatic microsomal mixed function oxidases (3632, 3807). Within 24 hrs of administering TEL to rats, 50% of the lead in blood is the metabolite, triethyl lead, and within 7 days all lead is triethyl lead; the half-life of triethyl lead in rat blood is about 10 days (3073, as cited in 3340). In rabbits and mice the half-life is much shorter (about 3 to 5 days), indicating that the residence time of triethyl lead in blood is species dependent (3340). Triethyl lead formed from TEL accumulates in tissues, with the highest levels found in liver, kidney, and brain (3340). Rats administered TEL by i.v. injection at 31 μmol/kg accumulated triethyl lead in liver and kidney, with a peak at 3 days; the level in brain peaked in 8 days with levels reaching 20 nmol/g wet weight and decreasing to 10 nmol/g at 16 days (3073, as cited in 3632). Jensen (3340) analyzed data presented for different species administered TEL by different routes and concluded that more lead accumulated in the brain of rats than of dogs, and multiple doses result in higher tissue levels than the same amount given as a single dose. One day after iv administration of 12 mg/kg of TEL to rabbits, triethyl lead accounted for 84% of the total lead in the liver, 68% in the kidney, and 59% in the blood (1264). As TEL is metabolized, the triethyl form is eventually converted to diethyl lead and finally to inorganic lead and excreted primarily via the urinary tract (1262, 1263, 3807).

Two studies reported the excretion of lead after exposure of rabbits to TEL. The total lead in the urine of rabbits administered TEL consisted of 69% diethyl lead, 27% inorganic lead, and 4% triethyl lead. Diethyl lead accounted for 93% of the total lead in the bile, and inorganic lead made up 90% of the colonic and rectal contents (1264). Kozarzewska and Chmielnicka (3574) studied the excretion pattern of diethyl lead in the urine of rabbits after exposure to TEL by gavage, iv injection, or inhalation. After administration of 12 mg/kg of TEL to rabbits by gavage, diethyl lead was excreted in urine; its maximum level of excretion occurred during the first day. Within the first 7 days diethyl lead comprised 70 to 90% of the total lead excreted and overall 76% of total lead excreted over 30 days. After iv administration of 12 mg/kg of TEL, diethyl lead comprised only 50% of the total lead excreted during the first 7 days and 40% of the total lead over a 30-day period. There was very little difference in the excretion of diethyl lead when the doses were reduced to

3 mg/kg. After both routes of exposure, diethyl lead comprised about 40% of the total lead excreted over a 30-day period. The total excretion of diethyl lead after inhalation exposure to 200 $\mu g/m^3$ for 5 hr was less than 20%.

According to Seawright et al. (3632) general acute clinical effects caused by TEL and triethyl lead include initial lethargy, followed by loss of appetite, tremors, hypermotility, hyperexcitability, and aggressiveness, and finally hypothermia, convulsions, incoordination, ataxia or paralysis, and death. Chester and Meyers (3120) reported that two doses of TEL at 150 mg/kg (ip) given to rats at 4 hr intervals caused diarrhea, lethargy, enopthalmia, ptosis, pink ears, and chromadacryorrhea. Rats given 17 mg/kg by gavage showed transient irritability, hypermotility, tremors, spasticity, and arched backs. Animals that survived for 2 weeks became asymptomatic, and animals given 1.7 mg/kg showed no effects (3619). Rats exposed to TEL by inhalation also showed signs of irritability, incoordination, aggressiveness, hyperactivity, and convulsions; whereas dogs showed signs of tremors, muscle twitching, hyperactivity, symptoms similar to chorea, and convulsions (3156). Kawamori et al. (1268) reported that a single ip doses of 10 mg/kg caused no effect in male rats, but doses greater than or equal to 20 mg/kg caused 80% mortality, with mean survival times ranging from 39.5 to 149.4 hr. The toxic signs included tremors, jumping, hyperexcitation, and tetanic convulsions. No significant changes in spontaneous motor activity were observed in surviving rats in the 10- and 20-mg/kg groups; however, the motor activity of dying rats in the 20- and 40-mg/kg groups significantly increased 5 to 7 days after administration. The oral LD_{50} was reported as 12.3 to 29 mg/kg (1265)

In a conclusion from their review regarding metabolism and toxicokinetics of organolead compounds, Jensen (3340) reported that the critical organ for organolead intoxications is the brain. In rats administered a single dose of TEL at 17 mg/kg, the major effect was in the cerebral cortex, accompanied by lesions in the spinal cord, oblongata, pons, and cerebellar cortex (3619). The types of lesions included damage to neurons (distortion of pyramidal and ganglion cells, shrinkage of the cytoplasm, some chromatolysis of Nissl's body, and pyknotic nuclei) with associated degeneration of the nerve tract. Damage to the neuroglia included increased metachromatic lipoprotein, gliosis, and vesiculation. Damage to the brain appendages involved blood vessels, ependymal cells, and leptomeninges. A dose of only 1.7 mg/kg resulted in much less damage only to the cerebral cortex. Rats and dogs exposed to TEL by inhalation showed similar brain lesions involving the cerebral cortex, the brain stem, and the medulla (3156).

Adult male rats treated with 7.88 mg/kg TEL subcutaneously at 7, 14 or 28 days prior to a single challenge with 35 mg/kg pentylenetetrazol, a seizure-inducing compound, had a significantly higher seizure rate than controls pretreated with saline. This suggests the possible involvement of the limbic system in the CNS toxicity of TEL (1269). The precise manner in which TEL alters brain function is not clearly known, but it may involve inhibition of monoamine oxidase (1254).

Komulainen et al. (3370) administered TEL to adult Wistar rats at doses of 30, 90, or 180 μmol/kg (10, 30, or 60 mg/kg) by gavage and measured monoamine (noradrenaline, dopamine, and 5-hydroxytryptamine) levels in various regions of the brain 24 hr after dosing. Noradrenaline levels showed a dose dependent decrease in the occipital cortex and an increase at 30 μmol/kg in the hypothalamus, a decrease at 180 μmol/kg, and no change at 90 μmol/kg. Dopamine and 5-hydroxytryptamine levels were not significantly affected by treatment. The also gave multiple doses of 3, 10, or 30 μmol/kg given at 2-day intervals for 10 doses and sacrificed the animals 24 hr after the last dose. Noradrenaline levels were significantly decreased at all doses in the corpus striatum. Dopamine and 5-hydroxytryptamine levels were both increased and decreased depending on the region of the brain and the dose. Two doses of TEL injected ip into adult male Sprague-Dawley rats caused a significant decrease in brain norepinephrine 2 to 20 hr after dosing (time of last measurement) (3120). Dopamine levels were significantly increased from 1 to 16 hr, with a peak at 4 hr. The levels of 5-hydroxytryptamine remained unchanged.

TEL caused an immunosuppressive effect in male mice exposed to 0.5-10 ppm in drinking water for 3 weeks. The maximal effect was produced at concentrations less than 2 ppm (1270).

The lowest lethal dose in rabbits after percutaneous administration is 830 mg/kg (47). When rabbits received a dermal application of 0.75 mg for 4 hours, tissue levels reached a peak after 18 hours, except in the spleen and bone where peak levels were reached after 7 and 30 days, respectively (1271).

TEL intoxication may cause impaired vision, weakness of the extrinsic muscles of the eye, increased mydriasis, loss of pupil reflex, optic neuritis and atrophy, and glaucoma (19). Grant tested TEL-containing gasoline in rabbit eyes and found it to cause immediate pain and blepharospasm which lasted for several minutes. When the application was repeated 10 times within a 5 minute period, it produced conjunctival hyperemia and moderate flocculent discharge, but no corneal or conjunctival damage (19).

54.3.1.4.2 Chronic Toxicity

In an oral study, rats were administered TEL by intragastric intubation at doses of 0.17 or 0.0017 mg/kg 5 days/week for 100 doses (3619). Body and organ weights were not significantly changed and the predominate organ showing lead accumulation was the liver followed by the kidney. Pathological lesions appeared in the telencephalon, myelencephalon, and medulla spinalis of the brain of animals given 0.17 mg/kg. These lesions were characterized by neuronal deformity, nuclear pyknosis, neuronophagia, nerve tract degeneration, focal gliosis, and nuclear vesiculation. At 0.0017 mg/kg neuronal damage was noted, but was not significantly more prevalent or severe than in controls.

In studies in which rats were given multiple inhalation exposures to TEL at concentrations of 12 mg/m^3 for 150 days, signs of toxicity and pathology appeared to

be related to the fate of the animals (fatality or survival), as well as to the duration of exposure (3156). Lesions appeared in the brain, liver, kidney and lungs.

No clinical manifestations of TEL toxicity were seen in rhesus monkeys given oral doses equivalent to 6 mg/kg/day of lead for 6 months. Minor elevations of blood and tissue lead were seen (1272).

54.3.2 Human and Epidemiologic Studies

54.3.2.1 Short-term Toxicologic Effects

The signs and symptoms of TEL intoxication differ from those of inorganic lead intoxication and are often vague and easily missed (46). The onset of symptoms may be delayed for up to 8 days after exposure. Acute exposure to TEL causes symptoms of CNS toxicity. Mild manifestations of intoxication include weakness, fatigue, headache, nausea, vomiting, diarrhea, anorexia, insomnia and weight loss. Peculiar symptoms are the sensation of hairs in the mouth and the feeling of insects crawling on the body. Ataxia, nystagmus or tremor may then develop. Vegetative disturbances known as the "TEL triad" begin to occur: hypotonia, hypothermia and bradycardia. As the intoxication worsens, there is confusion, delirium, manic excitement, catatonia, tonic-clonic convulsions or "organic weakness." The vegetative disturbances then become more pronounced. Loss of consciousness and death may follow after several days (1570). Severe intoxication causes recurrent or continuous episodes of disorientation and intense hyperactivity which may rapidly convert to convulsions that may terminate in coma or death (46, 1263). Absorption of only 1 g may be sufficient to cause death within 3-30 days due to its slow degradation to triethyl lead (1263). Unless death occurs, recovery is usually complete within approximately 1 week after mild intoxication, but may take up to 2 years after serious intoxication (3013, 3585 as cited in 3249).

The most pronounced acute histologic effects of TEL intoxication are in the brain. Neuronal death, which in not reversible because nerve cells do not regenerate, possibly causes deficiencies related to irreversible brain damage that is only partially or slowly compensated (3249). Neuronal death is especially prominent in the hypothalamic region of the brain (3585, as cited in 3249), but neuronal damage in other regions have been reported: the mammillary bodies in the floor of the fourth ventricle and in the quadrigeminal bodies (3066, as cited in 3249), basal ganglia, thalamus, and pons (3461, as cited in 3249). Other organs affected by acute TEL intoxication and the effects are congestion in the lungs, liver, and spleen and atrophy and lipoid depletion of the adrenal cortex (3249).

Another distinguishing feature of TEL intoxication is the normal or only slightly elevated blood lead and an abnormally high urinary lead. In severe intoxication, the urine lead is rarely less than 350 μg/L of urine, and blood lead is rarely greater than 50 μg/100g of blood (46). In addition, organically bound lead does not interfere with iron incorporation into protoporphyrin or with other stages of heme synthesis as shown by normal urinary levels of coproporphyrin, porphobilinogen, and

δ-aminolevulinic acid (1273). Also, there is a total absence of morphological or chemical abnormalities in the erythrocytes. These effects are all in contrast to those caused by inorganic lead (46).

Urinary lead is the most common means for detecting TEL intoxication, but diethyl lead may also be used as a specific indicator. Results obtained by Turlakiewicz and Chmielnicka (1274) showed a positive correlation between the concentration of TEL in the air and the amount of diethyl lead and total lead in the urine. These investigators suggested that permissible level of urinary diethyl lead in occupationally exposed workers should not exceed 8 μg/L.

The principal route of TEL intoxication in occupational exposure is by inhalation or absorption through skin (1254). Absorption of a sufficient quantity of TEL either briefly at a high rate (100 mg/m³ for 1 hr) or for prolonged periods at a lower rate causes acute intoxication (46).

TEL poisoning is often the result of accidental or intentional exposure to gasoline (1263); however, in one case of "massive" ingestion of pure TEL, the victim survived 36 hours. Initial signs and symptoms were referable to increased intracranial pressure, but death was due to pulmonary edema (1288).

In the case of gasoline exposure, it is uncertain which neurologic and psychiatric symptoms are caused by TEL and which by hydrocarbons in the fuel, but because of its longer half-life in the CNS (7 to 8 days in the brain), the symptoms have been attributed to TEL (1255, 1289). Individuals poisoned by "gasoline sniffing" manifests signs of encephalopathy, including irritability, anorexia, pallor, tremor, nausea, vomiting and delirium. The gasoline itself may cause acute pneumonitis. Death may occur from a combination of CNS depression, respiratory irritation, and bronchiolar obstruction (1289). Neurological effects include mixed choreoathetoid movements (i.e., ceaseless involuntary jerky or writhing movements) of the hands, arms, facial muscles, and extensor tendons of the feet (1289).

Coulehan et al. (1290) studied lead toxicity secondary to gasoline sniffing in 23 Navajo adolescents. Sixty-five percent of the cases first presented with toxic encephalopathy. Of 47 episodes, 31% involved asymptomatic lead overload; 31% involved tremor, ataxia, and other neurologic signs; and 38% involved encephalopathy, disorientation, and hallucinations. Blood lead levels were elevated, but no value exceeded 40 μg/dL.

Liquid TEL may penetrate the skin without producing appreciable local injury. TEL decomposition products in dust may cause itching, burning, and transient redness when in contact with moist skin or ocular membranes. TEL itself may be irritating to the eyes (54).

5.4.3.2.2 Chronic Toxicologic Effects

After chronic exposure to TEL, there may be a delay up to several years in the appearance of symptoms. Symptoms may appear gradually, with the only subjective complaints, such as weakness, fatigue, headaches, and insomnia. The TEL triad (hypotonia, bradycardia, and hypothermia) may appear, in addition to hyperhidrosis, sialorrhea, and tremors. The individual may also suffer from anorexia, weight loss, diarrhea, impotence, numbness in extremities, spasms in fingers and toes, throat ache, and deterioration of taste and smell. Neurotoxic effects of chronic TEL are manifested on the microscopic level by neuronal damage in the cerebral cortex (3585, as cited in 3249). Chronic exposure to TEL may also result in symptoms similar to those of inorganic lead poisoning as well as the CNS effects of acute organic lead intoxication (1263). Other symptoms are reported to include subtle behavioral alterations, such as reduction or absence of reactions to sound or light, loss of ability to concentrate, and reduction of memory. The long-term sequelae of these effects have not been assessed (1293). Chronic intoxication has mostly been diagnosed in workers exposed to aviation fuel or leaded gasoline.

Two epidemiology studies were found regarding human exposure to TEL. A mortality study conducted by (3600), consisted of 592 male workers (exposed group) employed at a plant producing tetraethyl lead and 660 white male workers (control group) employed at the same facility during the same time and having no known exposure to lead for more than 6 months. Occupational exposure was monitored so that urinary lead levels of the workers did not exceed 180 μg/L; annual means ranged from 70 to 100 μg/L, and the long-term mean was 90 μg/L. There were 51 deaths in the group exposed to tetraethyl lead and 68 in the unexposed group. The overall age-adjusted annual average mortality rate was 78/10,000 man-years for the exposed group and 72/10,000 for the unexposed group, compared with 126/10,000 for the general population. The total number of deaths attributed to cancer in the exposed group was eight (10.1 expected): two were lung tumors and one each was brain, eye, larynx, stomach, and urinary bladder, and one was a multiple myeloma. The number of cancer deaths were, in fact, less than expected. In the unexposed group, the total number of deaths attributed to neoplasms was 11; and one each was a kidney and a liver tumor, six were lung, two were urinary bladder, and one was a reticulum cell sarcoma. This study was not evaluated statistically. A comparison of 153 white male employees exposed to TEL for 20 or more years with a similar group of workers with no TEL exposure found skin cancer to be prevalent but the incidence in exposed workers was not significantly different from that of non-exposed workers (5% vs. 2.9%). IARC considers this study to be inadequate because workers who left employment for any reason were not included (1292, 1252).

A cause-specific mortality study consisting of a cohort of 2,510 male workers employed for at least 1 day at a plant producing tetraethyl lead was conducted by Sweeney et al. (3694). A total of 156 deaths occurred among males hired from 1952 to 1977. The SMR for deaths due to all causes was only 74. The SMRs were elevated (greater than 100), but were not statistically significant, for the following causes of death (observed/expected ratios in parenthesis): all malignant neoplasms

(38/36.95) and neoplasms of the colon and rectum (5/3.73), other digestive cancers (4/3.62), larynx (2/0.55), lung (14/12.47), brain (4/1.88), genitourinary system (3/2.26), and lymphatic and hematopoietic systems (2/1.52). The workers were also exposed to other chemicals, such as ethylene dibromide, ethylene dichloride, ethyl chloride, vinyl chloride monomer, dyes, and inorganic lead. Nevertheless, mortality due to all causes or to specific causes was not significantly increased.

54.3.3 Levels of Concern

The national interim primary drinking water standard for lead is 50 μg/L of water at the tap, and for drinking water at the source the proposed maximum contaminant level (MCL) is 5 μg/L of water (3742). Various drinking water standards and criteria have been established for lead. This concentration is also recommended for drinking water by the WHO (666) and for ambient water by the USEPA (3770).

OSHA (3539) has set a limit of 0.075 mg/m³ (as Pb) as the 8-hour work-shift exposure limit for TEL. The ACGIH (3005) recommends an exposure limit of 0.1 mg/m³ (as Pb). Both groups include a notation of possible skin absorption.

54.3.4 Hazard Assessment

All lead compounds are considered toxic, including the organolead compounds such as TEL. The toxicity of TEL is believed to be due to its metabolic conversion to triethyl and inorganic lead. TEL can be absorbed through the skin, inhaled as a vapor or ingested (17, 1255). Oral LD_{50} values for rats range from 12 to 29 mg/kg (47, 1265).

Few long-term animal studies are available for TEL. Rats repeatedly exposed to oral doses of 0.17 mg/kg of TEL exhibited neurotoxic effects (3619). Another study conducted with rhesus monkeys provided no indications of clinical effects subsequent to 6 months exposure to TEL (6 mg of Pb/kg/day) (1272). In humans, the short-term and long-term effects of TEL predominately affect the CNS resulting in irreversible neuronal damage and deficiencies, for which compensation occurs very slowly (3585, as cited in 3249).

Only one study regarding the carcinogenic effects of TEL was found; it showed induction of lymphomas in mice dosed at intervals between birth and weaning.

Limited mutagenicity studies indicate no dominant lethal effects in mice exposed to tetraethyl lead (1258). TEL is not teratogenic in either rats or mice with oral administration but is embryotoxic (1259, 1260).

In humans, although other organs may be affected, TEL toxicity is characterized primarily by neurotoxic effects, whether exposure is of short duration or long-term. Epidemiology studies did not show evidence of cancer or other chronic effects.

54.4 SAMPLING AND ANALYSIS CONSIDERATIONS

Determination of the concentration of TEL in soil and water requires collection of a representative field sample and laboratory analysis. Care is required to prevent losses during sample collection and storage. Soil and water samples should be collected in glass containers; extraction of samples should be completed within seven days of sampling and analysis completed within 30 to 40 days. In addition to the targeted samples, quality assurance samples such as field blanks, duplicates, and spiked matrices should be included in the analytical program.

TEL is not included among the EPA-designated priority pollutants, and an EPA-approved procedure for the analysis of TEL is not available. However, the recommended analytical methods for semivolatile organics, EPA Methods 625 (65) and 8250 (63), would be appropriate methods of choice for the analysis of TEL in aqueous (Method 625) or solid and waste (Methods 625 and 8250) samples. Prior to analysis, aqueous samples are extracted with methylene chloride using a separatory funnel or a continuous liquid-liquid extractor; solid samples are extracted with methylene chloride using soxhlet extraction or sonication methods. An aliquot of the concentrated sample extract is injected onto a gas chromatographic (GC) column using a solvent flush technique. The GC column is then programmed to separate the semivolatile organics; TEL is detected with a mass spectrometer. Neat and diluted organic liquids may be analyzed by direct injection of the sample.

A detection limit for TEL using these methods was not determined but would be in the range of 1 to 10 μg/L for aqueous samples and extracted non-aqueous samples and in the part-per-million (ppm) range for samples that have been directly injected.

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APPENDIX 1

USEFUL HANDBOOKS, DATABOOKS, RESPONSE GUIDES AND AIR FORCE DOCUMENTS

A listing of useful handbooks, databooks and response guides, all relating to the release of hazardous or toxic chemicals to the environment, the properties and hazards of the chemicals, initial responses to spills of such chemicals, or subsequent remedial action follow. The contents of each publication is briefly described. The following listing is not intended to be inclusive of all publications of this kind. However, it is felt that the acquisition and central location of these reports (at key Air Force offices) would provide a valuable resource.

- A Method for Determining the Compatibility of Hazardous Wastes

  Authors: H. K. Hatayama et al. (April 1980)

  Available from: U.S. Environmental Protection Agency
  Municipal Environmental Research Laboratory
  Cincinnati, OH
  (EPA Report No. EPA-600/2-80-076)
  (NTIS Report No. PB80-221005)

  Contents: Provides method and chart for defining compatibility of various families of hazardous materials and wastes.

- Accident Management Orientation Guide

  Authors: D. K. Shaver et al. (October 1983)

  Available from: Air Force Rocket Propulsion Laboratory
  Air Force Systems Command
  Edwards Air Force Base
  California 93523
  (Report No. AFRPL-TR-82-075)

  Contents: This document identifies guidelines for mitigating hazards associated with an in-service railroad derailment or a railroad yard accident involving hazardous materials of interest to the Air Force.

- Carbon Adsorption Isotherms for Toxic Organics

  Authors: R. A. Dobbs and J. M. Cohen (April 1980)

  Available from: U.S. Environmental Protection Agency
  Office of Research and Development
  Cincinnati, OH
  (EPA Report No. EPA-600/8-80-023)

  Contents: Provides detailed data on the effectiveness of carbon for removal of organic substances from water.

- Chemical Hazards of the Workplace

  Authors: N. H. Proctor and J. P. Hughes (1978)

  Available from: J. B. Lippincott Company
  Philadelphia, PA

  Contents: Provides data on the toxicological effects of chemicals and suggests medical treatment protocols in more detail than given elsewhere.

- CHRIS Hazardous Chemical Data

  Author: U.S. Coast Guard (1985)

  Available from: Superintendent of Documents
  U.S. Government Printing Office
  Washington, D.C. 20402
  (Stock No. 050-012-00147-2)

  Contents: Provides a wide variety of data on more than 1000 hazardous materials when ordered with various addendums. A separate volume (Stock No. 050-012-00158-8) provides graphs of temperature dependent physical properties.

- Dangerous Properties of Industrial Materials, 7th edition

  Author: N. I. Sax, ed. (1989)

  Available from: Van Nostrand Reinhold
  New York, NY

  Contents: A well-known handbook that provides a brief summary of the toxicology and properties of numerous hazardous substances.

- Dangerous Properties of Industrial Materials Report

  Author: N. I. Sax, ed. (bimonthly publication)

  Available from: Van Nostrand Reinhold Company
  New York, NY

  Contents: Each bimonthly report provides detailed data on the hazards and environmental effects of several chemicals. Much of the data is from the EPA's Oil and Hazardous Materials-Technical Assistance Data System (OHM-TADS) and similar sources.

- Emergency Action Guides

  Authors: P. C. Conlon and A. M. Mason, eds. (1984)

  Available from: Bureau of Explosives
  Association of American Railroads
  1920 L Street N.W.
  Washington, D.C. 20036

  Contents: Provides detailed data and spill response information on each of the 134 materials that comprise over 98 percent of the hazardous commodities transported by rail in the United States.

- Emergency Handling of Hazardous Materials in Surface Transportation

  Author: P. J. Student, ed. (1981)

  Available from: Bureau of Explosives
  Association of American Railroads
  1920 L Street N.W.
  Washington, D.C. 20036

  Contents: Provides brief spill response recommendations for each hazardous material regulated by the U.S. Department of Transportation.

- Emergency Response Guidebook

  Author: Materials Transportation Bureau (1987)

  Available from: U.S. Department of Transportation
  Materials Transportation Bureau
  Attention: DMT-11
  Washington, DC 20590
  (Publication DOT P5800.3)

  Contents: A guide for initial actions to be taken by emergency service personnel during hazardous material incidents.

- Fire Protection Guide on Hazardous Materials

  Author: National Fire Protection Association (1986)

  Available from: National Fire Protection Association
  Batterymarch Park
  Quincy, MA 02269

  Contents: Flash Point Index of Trade Name Liquids Fire Hazard Properties of Flammable Liquids, Gases, and Volatile Solids (NFPA 325M) Hazardous Chemicals Data (NFPA 49) Manual of Hazardous Chemical Reactions (NFPA491M)

- Groundwater Contamination Response Guide, Volume I: Methodology, Volume II: Desk Reference

  Authors: J. H. Guswa and W. J. Lyman (1983)

  Available from: National Technical Information Service
  Springfield, VA
  (as U.S. Air Force Report ESL-TR-82-39)
  or
  Noyes Publications
  Park Ridge, NJ
  (under the title "Groundwater Contamination and Emergency Response Guide" (1984))*

  Contents: Provides an overview of ground-water hydrology and a current technology review of equipment, methods, and techniques used to investigate incidents of ground water contamination by chemicals.

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*Noyes Publications also contain a reproduction of the report by A. S. Donnigian, Jr. et al.: Rapid Assessment of Potential Ground-Water Contamination Under Emergency Response Conditions, a 1983 report to the U.S. Environmental Protection Agency.

- Ground-Water Hydrology Workbook

  Authors: E.W. Artiglia and G.R. New (1984)

  Available from: USAF Occupational and Environmental Health Laboratory
  Brooks AFB, TX 78235
  (Report No. 84-168EQ111DGB)

  Contents: Summarizes introductory articles in ground-water hydrology of importance to base bioenvironmental engineers involved with the IRP program.

- Guidelines Establishing Test Procedures For The Analysis of Pollutants Under the Clean Water Act, Appendix A

  Author: U.S. Environmental Protection Agency (1984)

  Available from: Federal Register
  Volume 49(209):43234
  October 26, 1984

  Contents: Methods for analysis of environmental samples.

- Guidelines for the Selection of Chemical Protective Clothing

  Authors: A.D. Schwope et al. (1987)

  Available from: U.S. Environmental Protection Agency
  Washington, D.C.

  Contents: Denotes compatibility of rubber and plastic clothing materials with various chemicals; provides guidelines for clothing selection and use.

- Guidelines for the Use of Chemicals in Removing Hazardous Substances Discharges

  Authors: C. K. Akers, R. J. Pilie and J. G. Michalovic (1981)

  Available from: U.S. Environmental Protection Agency
  Office of Research and Development
  Cincinnati, OH
  (EPA Report No. EPA-600/2-81-205)

  Contents: Report provides guidelines on the use of various chemical and biological agents to mitigate discharges of hazardous substances.

- Handbook for Evaluating Remedial Action Technology Plans

  Authors: J. Ehrenfeld and J. Bass (1983)

  Available from: U.S. Environmental Protection Agency
  Office of Research and Development
  Cincinnati, OH
  (EPA Report No. EPA-600/1-83-076)

  Contents: Provides information on over 50 remedial action technologies for cleanup of chemically-contaminated sites.

- Handbook of Chemical Property Estimation Methods
  (subtitle: Environmental Behavior of Organic Compounds)

  Authors: W. J. Lyman, W. F. Rechl, D. H. Rosenblatt, eds. (1982)

  Available from: McGraw-Hill Book Co.
  New York, NY

  Contents: Provides estimation methods for (and discussion of) 26 environmentally-important properties of organic chemicals.

- Handbook of Environmental Data on Organic Chemicals, 2nd edition

  Author: K. Verschueren (1983)

  Available from: Van Nostrand Reinhold
  New York, NY

  Contents: Provides detailed property and environmental data on numerous organic substances.

- Handbook of Toxic and Hazardous Chemicals

  Author: M. Sittig (1985)

  Available from: Noyes Publications
  Park Ridge, NJ

  Contents: Discusses a wide range of topics for numerous chemicals, with special emphasis on toxicology and protective measures.

- Hazardous Chemicals Data Book, 2nd edition

  Author: G. Weiss, ed. (1986)

  Available from: Noyes Data Corporation
  Park Ridge, NJ

  Contents: Reproduction of data (physicochemical properties, hazards, toxicity, etc.) related to chemical spill response from (1) CHRIS Hazardous Chemical Data (1978) and (2) Material Safety Data Sheets prepared by Oak Ridge National Laboratory.

- Herbicide Handbook, 5th edition

  Author: Weed Science Society of America (1983)

  Available from: Weed Science Society of America
  309 West Clark Street
  Champaign, IL 61820

  Contents: Provides basic information on physiocochemical properties, uses, environmental fate, physiological and biochemical behavior, and toxicological properties for most herbicides in use. (Previous editions may cover out-of-use herbicides.)

- Manual for the Control of Hazardous Material Spills - Vol. 1: Spill Assessment and Water Treatment Techniques

  Authors: K. R. Huibregtse et al. (November 1977)

  Available from: U.S. Environmental Protection Agency
  Office of Research and Development
  Cincinnati, OH
  (EPA Report No. EPA-600/2-77-227)

  Contents: Provides both general and specific information on responding to spills of hazardous materials, particularly those into water.

- Methods to Treat, Control and Monitor Spilled Hazardous Materials

  Authors: R. J. Pilie et al. (1975)

  Available from: U.S. Environmental Protection Agency
  Industrial Waste Treatment Research Laboratory
  Edison, NJ
  (EPA Report No. EPA-670/2-75-042)

  Contents: Special studies of selected chemical spill response measures plus matrix of possible spill response measures for 250 hazardous liquids.

- NIOSH Manual of Analytical Methods, 3rd edition

  Author: Peter M. Eller, ed. (1984)

  Available from: Superintendent of Documents
  U.S. Government Printing Office
  Washington, D.C. 20402

  Contents: Contains sampling and analytical methods for use in industrial hygiene environmental monitoring.

- NIOSH/OSHA Occupational Health Guidelines for Chemical Hazards

  Authors: F. W. Mackison et al., eds. (January 1981)

  Available from: Superintendent of Documents
  U.S. Government Printing Office
  Washington, D.C. 20402
  (DHHS (NIOSH) Publication No. 81-123)

  Contents: Provides information on toxicology, chemical properties, first aid, and personal protective clothing and equipment for many OSHA-regulated commodities.

- Patty's Industrial Hygiene and Toxicology - Vol. 2A,B,C: Toxicology

  Authors: G.D. Clayton and F.E. Clayton, eds. (1981-1982)

  Available from: John Wiley & Sons
  New York, NY

  Contents: Provides extensive discussion of the properties and toxicology of numerous chemicals.

- Perry's Chemical Engineers Handbook

  Authors: R. H. Perry and D. Green, eds. (1984)

  Available from: McGraw-Hill Book Company
  New York, NY

  Contents: Contains extensive data on the properties of chemicals and on their compatibility with various materials of construction (plus numerous other topics).

- Pesticide Manual, 7th edition

  Author: C. R. Worthing, ed. (1983)

  Available from: British Crop Protection Council Publications
  Worcestershire WR13 15LP
  ENGLAND

  Contents: Provides a brief review of analysis, uses and toxicity of chemicals and microbial agents used as active components of pest-control products.

- Post Accident Procedures for Chemicals and Propellants

  - Interim Report for the Period 8/11/80 to 3/31/81 (September 1982) (Report No. AFRPL-TR-82-031)
  - Interim Report for the Period 4/81 to 1/82 (September 1982) (Report No. AFRPL-TR-82-032)
  - Guidelines Manual (January 1983) (Report No. AFRPL-TR-82-077)

  Authors: D. K. Shaver et al.

  Available from: Air Force Rocket Propulsion Laboratory
  Air Force Systems Command
  Edwards Air Force Base
  California 93523

  Contents: This is a series of manuals providing information and data required to respond to spills of chemicals and propellants of special interest to the Air Force.

- Quality Criteria for Water

  Author: U.S. Environmental Protection Agency (July 1976)

  Available from: Superintendent of Documents
  U.S. Government Printing Office
  Washington, D.C. 20402
  (Stock No. 055-001-01049-4)

  Contents: This is EPA's well-known guide to water quality criteria commonly referred to as the "redbook."

- Registry of Toxic Effects of Chemical Substances

  Authors: R. L. Tatken and R. J. Lewis, Sr., eds. (June 1983)

  Available from: Superintendent of Documents
  U.S. Government Printing Office
  Washington, D.C. 20402
  (DHHS [NIOSH] Publication 83-107)

  Contents: Summarizes results of primarily short-term toxicological experiments for thousands of chemicals.

- Standard Methods for the Examination of Water and Wastewater, 15th edition

  Authors: Arnold Greenberg et al., eds. (1985)

  Available from: American Public Health Association
  1015 18th Street
  Washington, D.C.

  Contents: Methods for analysis of environmental samples.

- Supplement to Development Document, Hazardous Substances Regulations, FWPCA as Amended 1972

  Author: U.S. Environmental Protection Agency (November 1975)

  Available from: U.S. Environmental Protection Agency
  Office of Water Planning and Standards
  Washington, D.C. 20460

  Contents: Discusses the environmental effects of numerous water pollutants.

- Test Methods for Evaluating Solid Waste-Physical Chemical Methods, 3rd edition

  Author: U.S. Environmental Protection Agency (1987)

  Available from: Superintendent of Documents
  U.S. Government Printing Office
  Washington, D.C. 20460
  (Report No. SW-846)

  Contents: Methods for analysis of environmental samples.

- TLVs-Threshold Limit Values for Chemical Substances and Physical Agents in the Work Environment and Biological Exposure Indices with Intended Changes for 1987-1988

  Author: American Conference of Governmental Industrial Hygienists (1987)

  Available from: American Conference of Governmental Industrial Hygienists
  6500 Glenway Ave., Bldg. D-5
  Cincinnati, OH 45211

  Contents: This booklet (or the latest version of it) presents recommended exposure limits for airborne concentrations of toxic materials in the working environment.

- Toxicology of the Eye

  Author: W. M. Grant (1986)

  Available from: Charles C. Thomas - Publisher
  Springfield, IL

  Contents: An excellent source of information on the effects of numerous chemicals and other substances on the eyes.

- USAF OEHL Recommended Sampling Procedures

  Author: USAF Occupational and Environmental Health Laboratory (January 1982)

  Available from: USAF Occupational and Environmental Health Laboratory
  Brooks AFB, TX 78235
  (Limited Distribution)

  Contents: Outlines standardized sampling procedures with appropriate collection and preservation techniques for submission of samples to USAF OEHL for analysis.

- Water-Related Environmental Fate of 129 Priority Pollutants (2 volumes)

  Authors: M. A. Callahan et al. (December 1979)

  Available from: U.S. Environmental Protection Agency
  Washington, D.C.
  (EPA Report No. EPA-440/4-79-029a and -029b)
  (NTIS No. PB80-204373 and PB80-204381)

  Contents: Individual chapters address the fate of priority pollutants in the environment.

PERTINENT AIR FORCE PUBLICATIONS FOR THE USAF INSTALLATION RESTORATION PROGRAM

PUBLICATION	COMMENT
AFR 161-8	Establishes USAF permissible exposure limits for chemical substances.
AFR 161-17	Establishes USAF OEHL consultant services in Environmental Engineering, Industrial Hygiene, Occupational Health, Radiation Protection, and Analytical Chemistry.
AFR 161-44	Establishes USAF drinking water standards for common contaminants. For the most part, these are the same as the National Primary and Secondary Drinking Water Standards.
AFR 19-1	Establishes the USAF Environmental Protection Program.
AFR 19-7	Establishes responsibilities for environmental monitoring for Air Force installations. This regulation defines the roles of the Civil Engineer, the Bioenvironmental Engineer, and others with respect to environmental pollution monitoring.
DEQPPM 80-8	DoD implementation of RCRA.
DEQPPM 80-9	DoD guidance on the proper handling, storage, and disposal of PCB and PCB items.
DEQPPM 81-5	DoD guidance on the Installation Restoration Program to identify and evaluate past DoD hazardous material disposal sites on DoD installations and control migration from such sites.
EO 12088	Requires federal compliance with applicable federal, state, and local pollution control standards (procedural and substantiative) the same as any other industry or private person.
GWMR	Quarterly publication on ground-water monitoring remedial actions. Presents technical articles on contaminant transport, analytical methods, sampling methodology, and data interpretation.
IRPMC	Establishes the management concept for the IRP Phase II program.
LEEV LTR	Policy letters formulated by USAF HQ/LEEV.

NCP	Establishes procedures for response to potential for confirmed contamination of our nation.

APPENDIX 2

U.S. AIR FORCE POINTS OF CONTACT FOR THE INSTALLATION RESTORATION PROGRAM

- Mr. Gary D. Vest
  Maj. Patrick T. Fink
  SAF/MIQ
  Washington, D.C. 20330-5000
  AV 227-9297
  Commercial: (202) 696-9297

  Office of the Assistant Secretary of the Air Force
  Deputy for Environment and Safety

  Responsible for overall Air Force IRP guidance.

IRP GROUP

- Maj. Scott [illegible]. Smith, Branch Chief
  AV 297-0275
  Responsible for IRP engineering policy formulation.

- Maj. Roy K. Soloman
  AV 297-0275
  Responsible for Environmental Compliance Assessment and Management Program (ECAMP), Environmental Protection Committee, and IRP implementation.

- Col. Raymond A. Malinovsky
  Chief, Environmental Quality Division
  Director of Engineering and Services
  HQ USAF/LEEV
  Bolling Air Force Base
  Washington, DC 20332-5000

- Capt. Gerald L. Hromowyk
  AV 297-0275
  Responsible for spill policy and management information systems.

- Capt. Charles M. Groover
  AV 297-0275
  Responsible for underground storage tanks and training.

- Mr. Earl E. Kneeling
  AV 297-4174
  Responsible for Defense Environmental Restoration Program policy.

- Mr. Jeffery J. Short
  AV 297-0275
  Responsible for Third Party Sites.

- Col. Thayer J. Lewis, Chief
  Bioenvironmental Engineering
  HQ USAF/SGPA
  Bolling AFB, DC 20332-6188
  AV 297-1737
  Commercial: (202) 767-1737

- Lt. Col. Edward W. Artiglia
  AV 297-1738
  Responsible for IPR medical service policy formulation.

- Col. Frank P. Gallagher
  HQ AFESC/RDV
  Tyndall AFB, FL 32403-6001
  AV 970-2097/2098
  Commercial: (904) 283-2097/2098

  USAF Engineering and Services Center
  Engineering and Services Laboratory
  Environics Division

  Responsible for IRP engineering research and development.

- Mr. Emile Y. Baladi
  USAF OEHL/TS
  Brooks AFB, TX 78235-5000
  AV 240-2158/2159
  Commercial: (512) 536-2158/2159

  USAF Occupational and Environmental Health Laboratory Technical Services Division

  Responsible for IRP Phase II technical program management.

- Dr. Jeffrey W. Fisher
  AAMRL/THA
  Wright-Patterson AFB, OH 45433-6573
  AV 785-2704
  Commercial: (513) 255-2704

  Harry G. Armstrong Aerospace Medical Research Laboratory Toxic Hazards Division

  Responsible for IRP health effects research.

- Lt. Col. Stanley O. Hewins
  USAF OEHL/ECO
  Brooks AFB, TX 78235-5000
  AV 240-2063
  Commercial: (512) 536-2063

  USAF Occupational and Environmental Health Laboratory Consultant Services Division
  Environmental Health Branch

  Responsible for Toxicology Consultant Service.

- Major Air Command Bioenvironmental Engineers
  See latest edition of the "Worldwide Listing of Bioenvironmental Engineering and Environmental Health Personnel."

  Responsible for implementing IRP policy and management decisions and coordinating with state/local regulatory agencies.

APPENDIX 3

MATH, CONVERSIONS AND EQUIVALENTS

- Calculation of Air W/V Conversion Factors

One liter of air at 25 °C (298.16 °K) contains:

$$\frac{(1 \text{ atm})(1 \text{ liter})}{(.0821 \text{ liter atm/mole})(298.16 \text{ °K})} = 0.040874 \text{ moles of gas.}$$

Hence, one liter of air contains:

MW x 10^{-4} x 0.040874 grams of a contaminant at 1 ppm.

This is the same as saying 1 m^3 of air contains:

MW x 0.040874 mg of a contaminant at 1 ppm.

For example, chloroform has a MW of 119.39. Thus,

1 ppm = 119.39 x 0.040874 ≈ 4.88 mg/m^3 at 25°C.

- Conversion for Solutes in Water

1 mg/L ≈ 1 ppm (by weight).

- Conversion of Percent in Food, Water or Air to Parts Per Million

X% = X parts per 100 parts

$$\frac{X}{100} (10^6) = \text{ppm.}$$

- Conversion of Parts Per Million in Food or Water to mg/kg bw/day

Since both food intake and body weight vary with age (and some times, with treatment), there is no single factor that precisely converts parts per million (ppm) in food or water to mg/kg body weight/day. However, by assuming 100% absorption and adopting a set of standard values for each species for daily food, water and air intake

and average body weight, one can convert a ppm dosage level, within reasonable limits, to mg/kg bw/day for the sake of comparisons.

The following standard body weights and intake values were used to convert dietary or respiratory intakes to estimated daily dose rate:

Species	Body Weight (kg)	Food Consumption (g/day)	Approximate Water Intake (mL/day)	Minute Volume (m^3/min)
Human	70	700	2000	7.4×10^{-3}
Mouse	0.025	3	4.5	2.3×10^{-5}
Rat	0.3	15	20	1.0×10^{-4}
Monkey	5	250	500	8.6×10^{-4}
Rabbit	2	60	330	1.1×10^{-3}
Dog	10	250	500	5.2×10^{-3}
Guinea pig	0.5	30	85	1.6×10^{-4}

For example, at a dietary concentration of 1 ppm of Chemical X, an average adult mouse would consume 3 g of food per day or 0.12 mg of Chemical X/kg bw/day. This value was calculated as follows:

Intake (mg/kg bw/day) = food consumption (g/day) x dietary concentration (ppm) x $1g/10^6$ g diet x 1000 mg/g x 1/bw (kg).

- Calculation of Respiratory Uptake

Uptake (mg) = Concentration (mg/m^3) x minute volume (m^3/min) x retention factor (assume 1.0 unless value is known) x time (minutes).

- Temperature Conversions

The formulas given below were used to convert temperatures from one scale to another.

To convert temperatures given in Celsius to Fahrenheit:

$$°F = 9/5\ (°C) + 32$$

To convert temperatures given in Fahrenheit to Celsius:

$$°C = 5/9\ (°F - 32)$$

APPENDIX 4

STATE WATER QUALITY AGENCIES AND CONTACTS

Alabama

Department of Environmental Management
Water Division
1751 Dickinson Drive
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Department of Environmental Conservation
Water Quality Management Section
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Anchorage, AK 99503
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Wastewater & Water Treatment Section
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Charlene Denys

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Department of Environmental Quality
Safe Drinking Water Unit
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Phoenix, AZ 85034
(602) 257-2214

Arizona

Department of Environmental Quality
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Dave Woodruff

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Bill Keith

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Bob Macon

California

Water Resources Control Board
Division of Water Quality
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(916) 322-0212
Jessica Lacy/Fred La Caro

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Department of Health Services
Public Water Supply Branch
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Nadine Feletto/ David Spath

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Bill Wuerthel

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Marti Swicker

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Water Supply Section
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Henry Link/Steven Messer

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Division of Environmental
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(203) 566-7049
Jim Murphy

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Robert Hartman

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Jane Lane/Richard Howell

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John Davis

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Department of Consumer
and Regulatory Affairs
Water Quality Section
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Jim Collier

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Donald Behaven

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John Labie

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Kimes

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Randy Durham

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Bureau of Water Supply
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Phil Simmons

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Robert Stites

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The arrangement used in this index is based on the general molecular formula:

C_xH_y Element$_z$

where the order of elements is alphabetical. Inorganics precede carbon-containing compounds. Organics lacking hydrogen are listed before any CH's. Compounds without known molecular formulas are listed at the end of the index.

$CrO_4 \cdot 2Na$
Sodium chromate. See Chapter 53.

H_4N_2
Hydrazine. See Chapter 55.

CCl_3F
Trichlorofluoromethane. See Chapter 5.

CCl_4
Carbon tetrachloride. See Chapter 6.

CN
Cyanide. See Chapter 56.

$CHBr_2Cl$
Dibromochloromethane. See Chapter 3.

$CHCl_3$
Chloroform. See Chapter 4.

CH_2BrCl
Bromochloromethane. See Chapter 44.

CH_2Br_2
Dibromomethane. See Chapter 2.

CH_2Cl_2
Methylene chloride. See Chapter 1.

C_2Cl_2
Tetrachloroethylene. See Chapter 17.

C_2HCl_3
Trichloroethylene. See Chapter 16.

$C_2H_2Cl_2$
1,1-Dichloroethylene. See Chapter 14.
trans-1,2-Dichloroethylene. See Chapter 15.
1,2-Dichloroethylene, mixed isomers. See Chapter 15.
cis-1,2-Dichloroethylene. See Chapter 15.

$C_2H_2Cl_4$
1,1,2,2-Tetrachloroethane. See Chapter 11.

C_2H_3Cl
Vinyl chloride. See Chapter 13.

$C_2H_3Cl_3$
1,1,1-Trichloroethane. See Chapter 10.

$C_2H_4Br_2$
Ethylene dibromide. See Chapter 45.

$C_2H_4Cl_2$
1,1-Dichloroethane. See Chapter 8.
1,2-Dichloroethane. See Chapter 9.

C_2H_5Cl
Chloroethane. See Chapter 7.

$C_2H_6N_2O$
N-Nitrosodimethylamine. See Chapter 34.

$C_2H_6O_2$
Ethylene glycol. See Chapter 43.

$C_3H_6Cl_2$
1,2-Dichloropropane. See Chapter 12.

C_3H_6O
Acetone. See Chapter 40.

$C_3H_8O_2$
Methyl Cellosolve®. See Chapter 42.

$C_4H_8Cl_2O$
Bis(2-chloroethyl)ether. See Chapter 33.

C_4H_8O
Methyl ethyl ketone. See Chapter 41.

C_6HCl_5O
Pentachlorophenol. See Chapter 39.

$C_6H_3Cl_3$
1,2,4-Trichlorobenzene. See Chapter 28.

$C_6H_4Cl_2$
1,2-Dichlorobenzene. See Chapter 25.
1,3-Dichlorobenzene. See Chapter 26.
1,4-Dichlorobenzene. See Chapter 27.

$C_6H_4Cl_2O$
2,6-Dichlorophenol. See Chapter 38.

C_6H_5Cl
Chlorobenzene. See Chapter 24.

C_6H_5ClO
o-Chlorophenol. See Chapter 37.

C_6H_6
Benzene. See Chapter 18.

$C_6H_6Cl_6$
Lindane. See Chapter 47.

C_6H_6O
Phenol. See Chapter 36.

$C_7H_6N_2O_4$
2,6-Dinitrotoluene. See Chapter 23.

C_7H_8
Toluene. See Chapter 19.

$C_8H_5Cl_3O_3$
2,4,5-T. See Chapter 61.

$C_8H_6Cl_2O_3$
2,4-D. See Chapter 60.

C_8H_{10}
Ethyl benzene. See Chapter 20.
o-Xylene. See Chapter 21.

m-Xylene. See Chapter 21.
p-Xylene. See Chapter 21.
Xylenes, mixed. See Chapter 21.

$C_9H_{10}O$
2,4-Dimethylphenol. See Chapter 22.

$C_8H_{20}Pb$
Tetraethyl lead. See Chapter 54.

$C_8H_7Cl_3O_3$
2,4,5-TP. See Chapter 62.

$C_{10}H_6Cl_8$
Chlordane. See Chapter 48.

$C_{10}H_8$
Naphthalene. See Chapter 32.

$C_{10}H_{19}O_6PS_2$
Malathion. See Chapter 50.

$C_{12}H_4Cl_4O_2$
2,3,7,8-Tetrachlorodibenzo-p-dioxin. See Chapter 63.

$C_{12}H_{10}N_2O$
N-Nitrosodiphenylamine. See Chapter 35.

$C_{12}H_{14}O_4$
Diethyl phthalate. See Chapter 29.

$C_{12}H_{21}N_2O_3PS$
Diazinon® See Chapter 51.

$C_{14}H_8Cl_4$
DDE. See Chapter 59.

$C_{14}H_9Cl_5$
DDT. See Chapter 57.

$C_{14}H_{10}Cl_4$
DDD. See Chapter 58.

$C_{16}H_{22}O_4$
Di-n-butyl phthalate. See Chapter 30.

$C_{19}H_{20}O_4$
Butyl benzyl phthalate. See Chapter 46.

$C_{21}H_{21}O_4P$
Tri-o-cresyl phosphate. See Chapter 49.

$C_{24}H_{38}O_4$
Di(2-ethylhexyl)phthalate. See Chapter 31.

Molecular Formula Unknown

Aroclor ® congeners
See Chapter 52.

Automotive gasoline
See Chapter 65.

Fuel oils
See Chapter 66.

Hydraulic fluid
See Chapter 68.

JP-4
See Chapter 64.

Mineral base crankcase oil
See Chapter 69.

Stoddard solvent
See Chapter 67.

Synthetic crankcase oil
See Chapter 70.

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Mineral base crankcase oil	See Chapter 69
Synthetic crankcase oil	See Chapter 70

*Numeric designation assigned by the American Chemical Society's Chemical Abstracts Service which uniquely identifies a specific chemical compound.

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CZ4499000	26
CZ4500000	25
CZ4550000	27
DA0700000	20
DC2100000	28
EL6475000	41
FG4900000	6
FS9100000	4
GB2955000	53
GS7175000	56
GV4900000	47
HF3500000	63
HZ1800000	66
IQ0525000	34
JJ9800000	35
KH7525000	7
KH9275000	45
KI0175000	8
KI0525000	9
KI0700000	58
KI8575000	11
KJ2975000	10
KJ3325000	57
KL5775000	42
KN0875000	33
KU9625000	13
KV9360000	15
KV9400000	15
KV9422000	15
KV9450000	59
KW2975000	43
KX3850000	17
KX4550000	16
LS8950000	66
LX3300000	65
MU7155000	55

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OA5500000	66
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PA6360000	3
PA7350000	2
PA8050000	1
PB6125000	5
PB9800000	48
QJ0525000	32
SJ3325000	36
SK2625000	37
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TF3325000	51
TH9990000	46
TI0875000	30
TI1050000	29
TI1925000	31
TP4550000	54
TQ1315100	52
TQ1356000	52
TQ1360000	52
TQ1362000	52
TS8760000	56
TX9625000	12
UF8225000	62
VZ7525000	56
WJ8925000	67
WM8400000	50
XS5250000	19
XT1925000	23
YZ8061000	14
ZE2100000	21
ZE2190000	21
ZE2275000	21
ZE2450000	21
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No NIOSH Number Assigned:

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*A unique nine-position accession number (two letters and seven numerals) assigned alphabetically to each substance in the Registry of Toxic Effects of Chemical Substances published by the National Institute for Occupational Safety and Health (Reference 47).

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