TOXICOLOGICAL PROFILE FOR 1,1,2,2-TETRACHLOROETHANE

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

September 2008

DISCLAIMER

The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

UPDATE STATEMENT

A Toxicological Profile for 1,1,2,2-tetrachloroethane, Draft for Public Comment, was released in September 2006. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine/Applied Toxicology Branch
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Atlanta, Georgia 30333

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FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel

and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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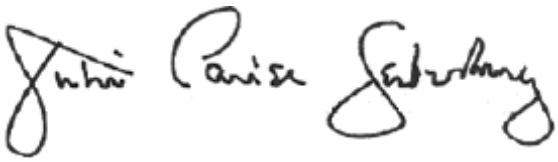

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*Legislative Background

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99 499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the Federal Register on December 7, 2005 (70 FR 72840). For prior versions of the list of substances, see Federal Register notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17,1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); February 28, 1994 (59 FR 9486); April 29, 1996 (61 FR 18744); November 17, 1997 (62 FR 61332); October 21, 1999(64 FR 56792); October 25, 2001 (66 FR 54014) and November 7, 2003 (68 FR 63098). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances will find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by type of health effect (death, systemic, immunologic, reproductive), by route of exposure, and by length of exposure (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Section 1.6	**How Can (Chemical X) Affect Children?**
Section 1.7	**How Can Families Reduce the Risk of Exposure to (Chemical X)?**
Section 3.7	**Children's Susceptibility**
Section 6.6	**Exposures of Children**

Other Sections of Interest:

Section 3.8	**Biomarkers of Exposure and Effect**
Section 3.11	**Methods for Reducing Toxic Effects**

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) ***Fax:*** (770) 488-4178
1-888-232-6348 (TTY)
E-mail: cdcinfo@cdc.gov ***Internet***: http://www.atsdr.cdc.gov

The following additional material can be ordered through the ATSDR Information Center:

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental*

Hazards; Skin Lesions and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity; and numerous chemical-specific case studies.

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs) provide answers to frequently asked questions about toxic substances.

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 200 Independence Avenue, SW, Washington, DC 20201 • Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-NIOSH.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212.

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific Minimal Risk Levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

3. Data Needs Review. The Applied Toxicology Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

4. Green Border Review. Green Border review assures the consistency with ATSDR policy.

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PEER REVIEW

A peer review panel was assembled for 1,1,2,2-tetrachloroethane. The panel consisted of the following members:

1. Paul C. Chrostowski, Ph.D., Principal, CPF Associates, Inc., Takoma Park, Maryland;

2. Jeffrey Fisher, Ph.D., Department Head and Professor, Department of Environmental Health Sciences, College of Public Health, University of Georgia, Athens, Georgia; and

3. Gary Ginsberg, Ph.D., Consultant in Environmental Toxicology and Risk Assessment, West Hartford, Connecticut.

These experts collectively have knowledge of 1,1,2,2-tetrachloroethane 's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about 1,1,2,2-tetrachloroethane and the effects of exposure to it.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites are then placed on the National Priorities List (NPL) and are targeted for long-term federal clean-up activities. 1,1,2,2-Tetrachloroethane has been found in at least 329 of the 1,699 current or former NPL sites. Although the total number of NPL sites evaluated for this substance is not known, the possibility exists that the number of sites at which 1,1,2,2-tetrachloroethane is found may increase in the future as more sites are evaluated. This information is important because these sites may be sources of exposure and exposure to this substance may be harmful.

When a substance is released either from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. Such a release does not always lead to exposure. You can be exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance, or by skin contact.

If you are exposed to 1,1,2,2-tetrachloroethane, many factors will determine whether you will be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with it. You must also consider any other chemicals you are exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT IS 1,1,2,2-TETRACHLOROETHANE?

Description	1,1,2,2-Tetrachloroethane is a synthetic, colorless, dense liquid that does not burn easily. It has a penetrating, sweet odor similar to chloroform.
Uses • **Manufacturing**	1,1,2,2-Tetrachloroethane production has decreased significantly in the United States. In the past, it was used in large amounts to produce other chemicals and as an industrial solvent. 1,1,2,2-Tetrachloroethane was also used to separate fats and oils from other substances, to clean and degrease metals, and in paints and pesticides. Less toxic chemicals are now available to replace this solvent, and large-scale commercial production has stopped, although some production still occurs. It is presently used as a chemical intermediate, and information about this use is limited.

For more information on the physical and chemical properties of 1,1,2,2-tetrachloroethane and its production, disposal and use, see Chapters 4 and 5.

1.2 WHAT HAPPENS TO 1,1,2,2-TETRACHLOROETHANE WHEN IT ENTERS THE ENVIRONMENT?

Sources	Most 1,1,2,2-tetrachloroethane released into the environment eventually moves into the air or groundwater. Most of the 1,1,2,2-tetrachloroethane released to soil or land will evaporate back to the air. If released on the land, 1,1,2,2-tetrachloroethane does not tend to attach to soil particles. When released to surface water, much of the chemical will evaporate back to the air, while the remainder may break down due to reactions with water. Similar reactions can take place in soils and sediments.
How 1,1,2,2-tetra-chloroethane breaks down	Most 1,1,2,2-tetrachloroethane is expected to disappear from groundwater and air in about 1 year. 1,1,2,2-Tetrachloroethane breaks down by losing chlorine atoms. The resulting chemicals may also pose a health hazard. It has been estimated that 1,1,2,2-tetrachloroethane should not build up significantly in the bodies of fish or other aquatic organisms.

For more information on 1,1,2,2-tetrachloroethane in the environment, see Chapter 6.

1.3 HOW MIGHT I BE EXPOSED TO 1,1,2,2-TETRACHLOROETHANE?

General population	Exposure of the general population to 1,1,2,2-tetrachloroethane is expected to be very low based on the low concentrations reported for this substance in the environment. Individuals located near hazardous waste sites and facilities where this substance is used may be exposed to 1,1,2,2-tetrachloroethane in contaminated air, water, or soil.
Workplace	When a chemical such as 1,1,2,2-tetrachloroethane is used in making other chemicals, it is generally contained in closed automatic systems, which are not open to the air. Therefore, workers are not usually exposed to high levels of 1,1,2,2-tetrachloroethane.

For more information on human exposure to 1,1,2,2-tetrachloroethane, see Chapter 6.

1.4 HOW CAN 1,1,2,2-TETRACHLOROETHANE ENTER AND LEAVE MY BODY?

Enter your body • **Inhalation**	1,1,2,2-Tetrachloroethane can enter your body through the lungs.
• **Ingestion**	Most of the 1,1,2,2-tetrachloroethane in food or water will rapidly enter the body through the digestive tract.
• **Dermal contact**	1,1,2,2-Tetrachloroethane can also enter your body through the skin.
Leave your body	Once in your body, 1,1,2,2-tetrachloroethane is transformed into other chemicals called metabolites. Most of these other chemicals leave the body in the breath or urine within few days.

For more information on how 1,1,2,2-tetrachloroethane enters and leaves the body, see Chapter 3.

1.5 HOW CAN 1,1,2,2-TETRACHLOROETHANE AFFECT MY HEALTH?

This section looks at studies concerning potential health effects in animal and human studies.

General population • **Inhalation**	Breathing concentrated fumes of 1,1,2,2-tetrachloroethane (enough so that you notice its sickeningly sweet smell) can rapidly cause drowsiness, dizziness, nausea, and vomiting. Most people recover from these effects once they are in fresh air. Breathing high levels of 1,1,2,2-tetrachloroethane for a long time can cause liver damage.
• **Oral**	Drinking very large amounts of 1,1,2,2-tetrachloroethane can cause shallow breathing, faint pulse, decreased blood pressure, and possibly unconsciousness.
Laboratory animals • **Oral**	Oral exposure to very high doses of 1,1,2,2-tetrachloroethane can result in fatigue, difficulty breathing, and unconsciousness. Lower dose levels can result in liver damage.
Cancer	An increase in liver tumors was observed in mice following oral exposure. The EPA determined that 1,1,2,2-tetrachloroethane is a possible human carcinogen. The International Agency for Research on Cancer (IARC) determined that 1,1,2,2-tetrachloroethane is not classifiable as to human carcinogenicity.

Further information on the health effects of 1,1,2,2-tetrachloroethane in humans and animals can be found in Chapters 2 and 3.

1.6 HOW CAN 1,1,2,2-TETRACHLOROETHANE AFFECT CHILDREN?

This section discusses potential health effects in humans from exposures during the period from conception to maturity at 18 years of age.

Effects in children	There are no studies evaluating the effect of 1,1,2,2-tetrachloroethane exposure on children or immature animals. It is likely that children would have the same health effects as adults. We do not know whether children would be more sensitive than adults to the effects of 1,1,2,2-tetrachloroethane. It is possible that children are less strongly affected than adults because the ability of their body to convert 1,1,2,2-tetrachloroethane into more harmful products is immature.
Birth defects	Some effects have been observed in laboratory animals born to females exposed to 1,1,2,2-tetrachloroethane during pregnancy. This occurred at exposure levels that were also toxic to the mothers.
Breast milk	There is no information on levels of 1,1,2,2-tetrachloroethane in human breast milk.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO 1,1,2,2-TETRACHLOROETHANE?

Consumer products	Families are not likely to be exposed to amounts of 1,1,2,2-tetrachloroethane that are high enough to be a health concern because the chemical is no longer used in household products. It is possible that some old household products (such as cleaners, degreasers, and paints) contain small amounts of 1,1,2,2-tetrachloroethane; these products should be kept out of reach from children and used according to manufacturer's instructions.

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO 1,1,2,2-TETRACHLOROETHANE?

Detecting exposure	1,1,2,2-Tetrachloroethane breakdown products (metabolites) can be measured in blood and urine; however, these metabolites are common to several types of compounds.
Measuring exposure	The detection of 1,1,2,2-tetrachloroethane and/or its metabolites in your urine cannot be used to predict the kind of health effects that might develop from that exposure.

Information about tests for detecting 1,1,2,2-tetrachloroethane in the body is given in Chapters 3 and 7.

1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health. Regulations *can* be enforced by law. The EPA, the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA) are some federal agencies that develop regulations for toxic substances. Recommendations provide valuable guidelines to protect public health, but *cannot* be enforced by law. The Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH) are two federal organizations that develop recommendations for toxic substances.

Regulations and recommendations can be expressed as "not-to-exceed" levels, that is, levels of a toxic substance in air, water, soil, or food that do not exceed a critical value that is usually based on levels that affect animals; they are then adjusted to levels that will help protect humans. Sometimes these not-to-exceed levels differ among federal organizations because they used different exposure times (an 8-hour workday or a 24-hour day), different animal studies, or other factors.

Recommendations and regulations are also updated periodically as more information becomes available. For the most current information, check with the federal agency or organization that provides it.

Some regulations and recommendations for 1,1,2,2-tetrachloroethane include the following:

Drinking water	The EPA has determined that exposure to 1,1,2,2-tetrachloroethane in drinking water at a concentration of 0.04 mg/L for up to 10 days is not expected to cause any adverse effects in a child. The EPA has determined that lifetime exposure to 0.0003 mg/L 1,1,2,2-tetrachloroethane in drinking water is not expected to cause any adverse effects.
Workplace air	OSHA set a legal limit of 5 ppm 1,1,2,2-tetrachloroethane in air averaged over an 8-hour work day.

For more information on regulations and advisories, see Chapter 8.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below.

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

Toxicological profiles are also available on-line at www.atsdr.cdc.gov and on CD-ROM. You may request a copy of the ATSDR ToxProfiles™ CD-ROM by calling the toll-free information and technical assistance number at 1-800-CDC-INFO (1-800-232-4636), by e-mail at cdcinfo@cdc.gov, or by writing to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine
1600 Clifton Road NE
Mailstop F-32
Atlanta, GA 30333
Fax: 1-770-488-4178

Organizations for-profit may request copies of final Toxicological Profiles from the following:

National Technical Information Service (NTIS)
5285 Port Royal Road
Springfield, VA 22161
Phone: 1-800-553-6847 or 1-703-605-6000
Web site: http://www.ntis.gov/

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO 1,1,2,2-TETRACHLOROETHANE IN THE UNITED STATES

1,1,2,2-Tetrachloroethane is currently used as a chemical intermediate in the production of chlorinated hydrocarbons. In the past, this substance was used as an industrial solvent and extractant and was even a component of a few pesticide formulations; however, its manufacture and use as an end-product appears to have ceased in the United States. Present sources of 1,1,2,2-tetrachloroethane are largely attributable to fugitive emissions or discharges when it is generated as a byproduct and to emissions or discharges stemming from its production and use as a chemical intermediate.

1,1,2,2-Tetrachloroethane released onto soil is expected to partly volatilize, with the remainder leaching into the subsurface soil profile and, possibly, groundwater. Most of the 1,1,2,2-tetrachloroethane released to surface water is expected to volatilize, with the remainder dissolving in water where it would undergo degradation through hydrolysis and biodegradation. Degradation products include 1,1,2,2-trichloroethylene, 1,2-dichloroethylene, 1,1,2-trichloroethane, 1,2-dichloroethane, and vinyl chloride. In the ambient air, the dominant process for removal of 1,1,2,2-tetrachloroethane is the reaction with photochemically generated hydroxyl radicals. The half-life of this reaction is 54 days. Some 1,1,2,2-tetrachloroethane may diffuse upward into the stratosphere where it can participate in reactions that produce ozone-destroying chlorine radicals. However 1,1,2,2-tetrachloroethane is not expected to contribute significantly to the destruction of the ozone layer since <1% of the tropospheric 1,1,2,2-tetrachloroethane is predicted to reach the stratosphere.

Reported average concentrations of 1,1,2,2-tetrachloroethane measured in ambient air from both urban and rural locations across the United States are generally <10 ppt. However, average urban air concentrations as high as 57 ppb have been reported during the 1980's. More recent data are not available, but would be expected to be lower. As reported in the EPA STORET database for 1999–2006 (www.epa.gov/storet/dw_home.html), 1,1,2,2-tetrachloroethane was detected in approximately 43% of 12,476 water samples (surface water and groundwater), but only 3% of the samples contained 1,1,2,2-tetrachloroethane above the quantifiable limit. The range of quantifiable concentrations in these water samples was 0.1–25 ppb, with a mean of 0.6 ppb. 1,1,2,2-Tetrachloroethane was detected in

<0.001% of 166,599 public water system samples collected in the United States between 1993 and 1997. 1,1,2,2-Tetrachloroethane has not been detected in table-ready foods.

Based on the low levels of 1,1,2,2-tetrachloroethane measured in the environment and the decreased use of this substance in non-industrial settings, exposure of the general population to 1,1,2,2-tetrachloroethane is expected to be very low. However, individuals located near hazardous waste sites or facilities where 1,1,2,2-tetrachloroethane is used as a chemical intermediate may be exposed to this substance by inhalation of contaminated air, by ingestion of contaminated drinking water, or by dermal contact with contaminated soil. Contaminated air is the most likely source of potential exposure of the general population due to the relatively high volatility of 1,1,2,2-tetrachloroethane released to soil and surface water. Detection of 1,1,2,2-tetrachloroethane in the vicinity of an abandoned organic chemical manufacturing facility provides evidence for significant exposure from contaminated drinking water. Children are likely to be exposed to 1,1,2,2-tetrachloroethane by the same routes that affect adults. Occupational exposures are expected to occur primarily via inhalation and dermal contact.

1,1,2,2-Tetrachloroethane is well absorbed from the respiratory and gastrointestinal tracts in humans and laboratory animals, and absorption through the skin after dermal exposure has been demonstrated in animals. Following oral or inhalation exposure, 1,1,2,2-tetrachloroethane is extensively metabolized and excreted mainly as metabolites in the urine and breath. In rats and mice, 1,1,2,2-tetrachloroethane is metabolized to trichloroethanol, trichloroacetic acid, and dichloroacetic acid, which is then broken down to glyoxalic acid, oxalic acid, and carbon dioxide; a small percentage of the dose is exhaled in the breath as the parent compound. Both reductive and oxidative metabolism occurs, producing reactive radical and acid chloride intermediates, respectively.

2.2 SUMMARY OF HEALTH EFFECTS

A limited amount of information is available on the health effects of 1,1,2,2-tetrachloroethane in humans. The information in humans is generally very dated and incomplete and provides no information on dose-response. There has been only one epidemiological study involving this chemical and this study did not report on or classify exposure levels. However, the human database does suggest that 1,1,2,2-tetrachloro-ethane can target certain systems (nervous system, liver, mucous membranes) following high-dose exposure; it is also possible that more modern studies would be able to detect other types of effects in exposed populations. Reports of inhaled and ingested 1,1,2,2-tetrachloroethane indicate that central nervous system depression is the predominant effect of high-level acute exposure. Irritation of the

mucous membranes also has been observed following acute exposure to high concentrations of 1,1,2,2-tetrachloroethane vapor. Occupational studies suggest that repeated inhalation exposures can affect the liver as well as the nervous system; hepatic effects that have been reported include liver enlargement and jaundice.

Animal studies have clearly demonstrated that the central nervous system and liver are the main targets of 1,1,2,2-tetrachloroethane toxicity following acute- and intermediate-duration inhalation and oral exposure. Neurotoxicity has mainly been associated with near-lethal to lethal exposures; typical effects include a progression of clinical signs ranging from lethargy and incoordination to respiratory depression and loss of consciousness. Hepatic effects are prevalent at lower levels of exposure and include increases in serum enzymes and liver fat content, increased hepatic deoxyribonucleic acid (DNA) synthesis and mitotic activity, hepatocellular cytoplasmic vacuolation and other mild histological alterations, fatty degeneration, and hepatocellular necrosis. Chronic oral exposure to 1,1,2,2-tetrachloroethane induced liver cancer (hepatocellular carcinoma) in mice.

Little information is available on other effects of 1,1,2,2-tetrachloroethane. Reduced body weight gain and weight loss are effects of repeated oral exposures in rats and mice that generally occurred at high dose levels and, in dietary studies, were partly due to decreased food consumption from taste aversion. Intermediate-duration inhalation and oral exposures have been reported to cause hematological and immunological alterations in rats and rabbits. Chronic oral exposure to high doses induced kidney lesions (chronic inflammation and acute toxic nephrosis) in mice. Reproductive and developmental toxicity have not been adequately evaluated. Intermediate-duration oral exposure to doses that caused body weight loss also caused atrophy in reproductive tissues in male and female rats; alterations in sperm motility and estrus cycle of unclear toxicological significance were observed at lower doses. There were no effects on reproductive function in male rats following intermediate-duration inhalation of a low concentration of 1,1,2,2-tetrachloroethane, but testing of reproductive performance in female animals has not been conducted. Gestational exposure to 1,1,2,2-tetrachoroethane caused fetotoxicity in rats (decreased fetal body weight) and mice (litter resorptions) at oral doses that were maternally toxic, but fetuses were not examined for malformations.

A greater detailed discussion of 1,1,2,2-tetrachloroethane-induced neurological effects, hepatic effects and cancer follows. The reader is referred to Section 3.2, Discussion of Health Effects by Route of Exposure, for additional information on these effects and other health effects.

Neurological Effects. Acute inhalation exposure to high levels of 1,1,2,2-tetrachloroethane caused clinical signs of neurotoxicity in humans that included drowsiness, nausea, headache, and weakness, and at extremely high concentrations, unconsciousness and respiratory failure. A limited experimental study found similar effects (vertigo and fatigue) in two volunteers who were exposed to 146 ppm for 30 minutes or 336 ppm for 10 minutes, which are levels that also caused irritation of the mucous membranes.

In animals that inhaled 1,1,2,2-tetrachloroethane, clinical signs of neurotoxicity (e.g., incoordination, loss of reflexes, labored respiration, prostration, and loss of consciousness) typically preceded death, which occurred at concentrations as low as 1,000–1,168 ppm for 1.5–4 hours in rats and mice. A sublethal exposure of 576 ppm for 30 minutes caused reduced activity and alertness in rats and guinea pigs. The effective concentration for a 50% decrease in spontaneous motor activity in rats was 360 ppm for a 6-hour exposure. Intermediate-duration intermittent exposure to high concentrations of 1,1,2,2-tetrachloroethane caused neurological effects in mice similar to those observed in acute studies. Data on the neurotoxicity of single or repeated daily exposures to low levels of 1,1,2,2-tetrachloroethane vapor were not located.

Information on the neurotoxicity of oral exposure to 1,1,2,2-tetrachloroethane in humans is available from case reports. People who intentionally ingested a lethal amount usually lost consciousness within approximately 1 hour and died 3–20 hours postingestion. No deaths occurred in patients who were accidentally given an estimated oral dose of 68–118 mg/kg as medicinal treatment for hookworm, although they experienced loss of consciousness and other clinical signs of narcosis that included shallow breathing, faint pulse, and pronounced lowering of blood pressure. In animals, lethargy and central nervous system depression occurred in rats gavaged with 270–300 mg/kg/day for 1–12 days or 208 mg/kg/day for 21 days. Information on neurological effects of lower acute oral doses are limited to a poorly reported rat study in which a single gavage dose of 100 mg/kg caused ataxia and 50 mg/kg caused decreased passive avoidance to an electric shock, possibly due to an increased threshold of shock perception due to a subtle anesthetic effect. In studies of dietary (nonbolus) exposure, no clinical signs of neurotoxicity occurred in rats and mice that were exposed to 320 and 1,400 mg/kg/day, respectively, for 14 weeks. Comprehensive neurobehavioral evaluations (functional observational batteries, FOBs) in these studies showed no effects at doses as high as 80 mg/kg/day in the rats and 700 mg/kg/day in the mice (higher doses not evaluated).

Hepatic Effects and Cancer. Some humans exposed to 1,1,2,2-tetrachloroethane vapors in the workplace have developed jaundice and an enlarged liver. Specific clinical signs were not associated with specific exposure levels, although vapor concentrations in one study ranged from 1.5 to 248 ppm.

Liver cirrhosis was not increased in an epidemiological study of men occupationally exposed to unmeasured levels of 1,1,2,2-tetrachloroethane fumes in a clothing plant. Liver congestion and necrosis were observed in the autopsies of three humans who died following inhalation or oral exposure to 1,1,2,2-tetrachloroethane.

Information on the hepatotoxicity of inhaled 1,1,2,2-tetrachloroethane includes gross observations of fatty degeneration in rats, mice, and guinea pigs that died following acute- or intermediate-duration intermittent exposures to ≥1,000 ppm concentrations. Studies in which rats were exposed to lower concentrations of 1,1,2,2-tetrachloroethane for 4 hours, 4 hours/day for 8 of 10 days, or 5 days/week for 15 weeks found generally mild hepatic effects as indicated by clinical chemistry and histological alterations, but reporting limitations, insufficient quantitative data, and other study inadequacies preclude identification of reliable effects levels. Effects in these studies included increases in serum enzymes, increases in serum and liver triglycerides, changes in serum protein fractions, and fine droplet fatty degeneration and cytoplasmic vacuolation.

Hepatic effects of oral exposure included hepatocellular degeneration in mice exposed to a lethal dietary dose of 2,394 mg/kg/day for 6 days, increased serum aspartate aminotransferase (AST) in rats given a single gavage dose of 574 mg/kg, and increased liver cell DNA synthesis, mitotic activity, and centrilobular swelling in rats and/or mice exposed to 75–300 mg/kg/day by gavage for 4 days. Liver effects in intermediate-duration studies included cytoplasmic vacuolation in rats exposed to 104 mg/kg/day by gavage for 21 days, and hepatocellular degeneration in mice exposed to 337.5 mg/kg/day by gavage for 16 days or 599 mg/kg/day in the diet for 15 days. Comprehensive 14-week dietary studies showed that the liver was the most sensitive target of 1,1,2,2-tetrachloroethane toxicity for intermediate-duration exposure in rats and mice. Hepatic effects in the rats included biologically significant increases in serum alanine aminotransferase (ALT), sorbitol dehydrogenase (SDH), alkaline phosphatase (ALP) and bile acids, hepatocyte necrosis, bile duct hyperplasia, and liver pigmentation at 170–320 mg/kg/day. Hepatic effects in the mice included biologically significant increases in serum ALT and SDH, and necrosis, pigmentation, and bile duct hyperplasia at ≥300 mg/kg/day.

In the only chronic study of 1,1,2,2-tetrachloroethane, rats were exposed to time-weighted average (TWA) doses of 0, 62, or 108 mg/kg/day (males) or 0, 43, or 76 mg/kg/day (females) by gavage on 5 days/week for 78 weeks, followed by an observation period of 32 weeks. Fatty degeneration of the liver occurred at 108 mg/kg/day, but no significant increases in tumor incidences were observed. Mice of both

sexes were similarly exposed to TWA doses of 0, 142, or 284 mg/kg/day for 78 weeks followed by 12 weeks of observation. Significant, dose-related increases in the incidence of hepatocellular carcinoma were observed in males (3/36, 13/50, and 44/49 in the control, low-dose, and high-dose groups, respectively) and females (1/40, 30/48, and 43/47, respectively). Based mainly on the results of this study, in an assessment conducted in 1994, the EPA has classified the carcinogenicity of 1,1,2,2-tetrachloroethane as Group C, possible human carcinogen. The International Agency for Research on Cancer (IARC) cancer classification for 1,1,2,2-tetrachloroethane is Group 3, not classifiable with regard to its carcinogenicity to humans. The National Toxicology Program (NTP) has not classified 1,1,2,2-tetrachloroethane for human carcinogenicity.

The mode of action of the hepatocarcinogenicity of 1,1,2,2-tetrachloroethane is incompletely characterized. It is likely that liver tumor formation by 1,1,2,2-tetrachloroethane involves its metabolism to one or more active compounds, although there is no direct evidence linking one or more metabolites to its carcinogenic effects. Genotoxicity studies provide only limited evidence of a genotoxic mode of action. 1,1,2,2-Tetrachloroethane has weak genotoxic activity, with *in vitro* genotoxicity tests generally reporting negative results except for assays of sister chromatid exchange (SCE) and cell transformation; *in vivo* tests of genotoxicity have shown a similar pattern.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for 1,1,2,2-tetrachloroethane. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic

bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

Inhalation MRLs

No acute-duration inhalation MRL has been derived for 1,1,2,2-tetrachloroethane due to insufficient data. Reports in humans indicate that high-dose acute inhalation exposure to 1,1,2,2-tetrachloroethane can cause central nervous system depression and mucous membrane irritation (Coyer 1944; Hamilton 1917; Lehmann and Schmidt-Kehl 1936), but exposure-response data are lacking or insufficient. The preponderance of information on the acute inhalation toxicity of 1,1,2,2-tetrachloroethane in animals pertains to neurological and hepatic effects of near-lethal to lethal exposures to concentrations above approximately 1,000 ppm (Carpenter et al. 1949; Horiuchi et al. 1962; NIOSH 1978; Pantelitsch 1933; Schmidt et al. 1980b). The lowest effective concentration for a serious neurotoxic effect (50% decrease in spontaneous motor activity) was 360 ppm for 6 hours in rats (Horvath and Frantik 1973). No information is available on neurotoxicity at lower concentrations, precluding identification of a less-serious lowest-observed-adverse-effect level (LOAEL) or no-observed-adverse-effect level (NOAEL). Hepatic effects that include histological alterations and serum and liver biochemical changes have been reported in studies of rats exposed to concentrations as low as 60 ppm for 4 hours (Schmidt et al. 1980b) and 2.2 ppm for 4 hours/day for 8 of 10 days (Gohlke and Schmidt 1972; Schmidt et al. 1972), but these studies are inadequate for identifying a reliable NOAEL or LOAEL and deriving an acute inhalation MRL due to insufficient data on incidence, magnitude, and/or severity of effects.

No intermediate-duration inhalation MRL has been derived for 1,1,2,2-tetrachloroethane due to insufficient data. Intermittent intermediate-duration exposure to lethal concentrations of 1,1,2,2-tetrachloroethane (7,000–9,000 ppm) caused central nervous system depression and fatty liver degeneration in rats and mice (Horiuchi et al. 1962). Information on effects of lower concentrations of 1,1,2,2-tetrachloroethane is available from poorly reported studies in rats and rabbits (Kulinskaya and Verlinskaya 1972; Schmidt et al. 1972; Shmuter 1977; Truffert et al. 1977; Union Carbide Corporation 1947). Findings in these studies included transient histological alterations in the liver of rats exposed to 560 ppm for 5 hours/day, 5 days/week for 15 weeks (Truffert et al. 1977), hematological alterations and increased liver fat content in rats exposed to 1.9 ppm for 4 hours/day for 265 days (Schmidt et al. 1972), alterations in serum acetylcholinesterase activity in rabbits exposed to 1.5 ppm for 3 hours/day, 6 days/week for 7–8.5 months (Kulinskaya and Verlinskaya 1972), and immunological alterations in rabbits exposed to 0.3–14.6 ppm for 3 hours/day, 6 days/week for 8–10 months (Shmuter 1977). None of these studies are

adequate for identification of reliable NOAELs or LOAELs or MRL derivation due to insufficient data on incidence, magnitude, and/or severity of effects and other reporting limitations.

No chronic-duration inhalation MRL has been derived for 1,1,2,2-tetrachloroethane due to insufficient data. Information on the chronic inhalation toxicity of 1,1,2,2-tetrachloroethane in humans is available from several occupational studies (Jeney et al. 1957; Lobo-Mendonca 1963; Minot and Smith 1921; Norman et al. 1981) that are inadequate for identification of effect levels due to limitations that include insufficient characterization of exposure levels, lack of control data, dermal exposures, and/or mixed chemical exposures. Although not sufficient for identification of effect levels or MRL derivation, the occupational studies provide limited supporting information on the neurotoxicity and hepatotoxicity of 1,1,2,2-tetrachloroethane. Chronic inhalation studies in animals have not been performed.

Oral MRLs

No acute-duration oral MRL has been derived for 1,1,2,2-tetrachloroethane due to insufficient data. Single oral doses in the range of 68–118 mg/kg are estimated to be serious LOAELs for neurotoxicity in humans based on unconsciousness and other clinical signs observed in case reports (Hepple 1927; Lilliman 1949; Mant 1953; Sherman 1953; Ward 1955). The preponderance of information on the acute oral toxicity of 1,1,2,2-tetrachloroethane in animals is provided by gavage studies in rats and mice exposed to near-lethal to lethal dose levels. Rats were more sensitive than mice and the nervous system was more sensitive than the liver. Central nervous system depression and death, but no clearly adverse effects in the liver, occurred in rats exposed to gavage doses as low as 270–300 mg/kg/day for 1–4 days or 208 mg/kg/day for 13–14 days (Hanley et al. 1988; NTP 1993a, 1993b, 1996). Information on effects of lower acute oral doses in animals is limited to a rat study in which a single gavage dose of 100 mg/kg caused ataxia and 50 mg/kg caused decreased passive avoidance to an electric shock, possibly due to an increased threshold of shock perception due to a subtle anesthetic effect (Wolff 1978). The possible anesthetic effect suggests that 50 mg/kg is a LOAEL for neurotoxicity in rats, but evaluation of the study and the significance of the effect level is complicated by incomplete reporting and insufficient quantitative data. Derivation of an acute MRL is precluded by the uncertain reliability of the 50 mg/kg/day LOAEL in rats and, particularly, its proximity to the 68–118 mg/kg doses causing serious neurotoxicity in humans.

- An MRL of 0.5 mg/kg/day has been derived for intermediate-duration (15–364 days) oral exposure to 1,1,2,2-tetrachloroethane.

Liver effects data from a comprehensive 14-week study in rats were used as the basis for an intermediate-duration oral MRL. In this study (NTP 2004a), groups of 10 male and 10 female F344 rats were exposed to diet containing 1,1,2,2-tetrachloroethane in reported average daily doses of 0, 20, 40, 80, 170, or 320 mg/kg/day for 14 weeks. The study was comprehensive in scope and included extensive evaluations of histology, clinical chemistry, and neurotoxicity (FOBs). Effects included increases in hepatic cytoplasmic vacuolization at 20 mg/kg/day, liver weight at 40 mg/kg/day, and hepatocellular hypertrophy at 80 mg/kg/day. These hepatic effects are not considered adverse because the severity of the vacuolation was minimal to mild and did not increase with dose, and the increases in liver weight and hepatocellular hypertrophy are considered adaptive responses to chemical exposure. Increases in serum ALT and SDH and decreases in serum cholesterol also occurred at ≥80 mg/kg/day, but the magnitudes of these changes were biologically significant only at ≥170 mg/kg/day. Other effects that occurred at 170 and 320 mg/kg/day included increases in serum ALP and bile acids, hepatocyte necrosis, bile duct hyperplasia, hepatocellular mitotic alterations, foci of cellular alterations, and liver pigmentation. As discussed by NTP (2004a), increases in serum ALT and SDH are specific markers of hepatocellular necrosis or increased cell membrane permeability (leakage) in rodents; increases in bile acids are markers of cholestasis, impaired hepatocellular function, or hepatocellular injury; increased ALP is another marker of cholestasis; and decreased serum cholesterol is possibly indicative of liver dysfunction (impaired cholesterol biosynthesis). There was no evidence of neurotoxicity, as shown by negative FOB testing at doses as high as 80 mg/kg/day (higher doses not tested) and lack of clinical signs in all dose groups. Additional information regarding the design and results of this study is presented in Appendix A. This study identified a NOAEL of 80 mg/kg/day and a LOAEL of 170 mg/kg/day for systemic toxicity based on adverse liver-related serum chemistry changes and histological manifestations of hepatocellular damage. This LOAEL is lower than or equal to the LOAELs for reproductive effects in males (320 mg/kg/day) and females (170 mg/kg/day). A LOAEL for neurotoxicity was not identified because there were no clinical signs of neurotoxicity or exposure-related findings in the FOB at doses as high as 80 mg/kg/day (highest tested dose in the FOB).

NTP (2004a) also tested mice in a similarly designed 14-week dietary study that supports the rat data in showing that the liver was the most sensitive target of 1,1,2,2-tetrachloroethane toxicity. Hepatic effects in the mice included minimal hepatocellular hypertrophy, increases in serum SDH, ALT, and bile acids, and decreased serum cholesterol at 160–200 mg/kg/day, and increases in serum ALP and 5'-nucleotidase, necrosis, pigmentation, and bile duct hyperplasia at 300–370 mg/kg/day. The magnitudes of the serum

chemistry changes were biologically significant at ≥300 mg/kg/day in females and ≥370 mg/kg/day in males. Based on the adverse serum chemistry and histopathological changes at 300 mg/kg/day and higher doses, this study identifies a LOAEL of 300 mg/kg/day for liver toxicity in mice; the corresponding NOAEL is 200 mg/kg/day. Additional information on the intermediate-duration oral toxicity of 1,1,2,2-tetrachloroethane is available from a 21-day gavage study in rats (NTP 1996), a 16-day gavage study in mice (NTP 1993d), 6-week gavage studies in rats and mice (NCI 1978), and 15-day diet studies in rats and mice (NTP 2004a). These studies are mainly dose range-finding studies that used small numbers of animals and had limited or no evaluations of clinical chemistry and histology. The lowest LOAELs in these studies were 100–104 mg/kg/day for reduced body weight gain and hepatocyte cytoplasmic vacuolation in rats exposed by gavage (NCI 1978; NTP 1996) and 337.5 mg/kg/day for hepatocellular degeneration in mice exposed by gavage (NTP 1993d). The NTP (2004a) 14-week dietary study is the best basis for MRL derivation because it tested wider ranges of doses and varieties of end points, identified lower LOAELs, and used a more relevant method of oral exposure than the other intermediate-duration studies.

The NTP (2004a) study found that the rat was more sensitive than the mouse, as reflected by the liver toxicity findings identifying a LOAEL and NOAEL that were lower in the rats (80 and 40 mg/kg/day) than in the mice (170 and 80 mg/kg/day). Potential points of departure for the intermediate-duration MRL were derived by benchmark dose (BMD analysis) of NTP (2004a) rat liver data. Data for liver weight, hepatocyte necrosis, and serum ALT, SDH, bile acids, and cholesterol in one or both sexes were selected for modeling because these end points showed statistically significant changes and best reflected the progression and spectrum of hepatotoxic effects. All available dichotomous models in the EPA Benchmark Dose Software (BMDS version 1.3.2) were fit to the incidence data for hepatocyte necrosis. The continuous-variable models in the software were applied to the data for changes in relative liver weight and serum ALT, SDH, bile acids, and cholesterol.

Appropriate model fits were obtained for the hepatocyte necrosis and serum bile acids data in both sexes and serum ALT and SDH data in males. A summary of the predicted BMDs and 95% lower confidence limits (BMDLs) using the best fitting models for these end points, as well as details of the BMD modeling, are presented in Appendix A. For the hepatocyte necrosis incidence data, predicted doses associated with 30, 20, 10, 5, and 1% extra risks were calculated as possible alternative benchmark responses (BMRs) for the best fitting model. Conventionally, a 10% extra risk has served as a point of departure for MRL determination. However, because the NTP (2004a) study examined only 10 animals per group, the limit of detection is above the 10% level, likely in the 20–30% range. For the continuous

data, the calculated BMDs and BMDLs are estimates of the doses associated with a change of 1 standard deviation from the control. Predicted doses associated with an increase of 100% (i.e., 2-fold) were also calculated for the best fitting model for the changes in liver enzymes (serum ALT and SDH), as an increase of this magnitude is sometimes considered to be an indicator of clinical significance for these effects.

The lowest BMDLs were calculated for the male rat serum ALT and SDH data using 1 standard deviation below the control mean as the BMR. The BMDLs for serum ALT (26.56 mg/kg/day) and serum SDH (25.13 mg/kg/day) are approximately half of the BMDL of 53.88 mg/kg/day calculated using the female rat hepatocyte necrosis incidence data and a BMR of 10%. The BMDLs for the serum enzyme changes appear to be overly conservative predictions that have questionable biological plausibilty because they are substantially below the study NOAEL of 80 mg/kg/day. Effects occurring at the NOAEL included increases in serum ALT and SDH that were not adverse and hepatocyte necrosis in 1/10 females. The BMDL10 of 53.88 mg/kg/day for minimal hepatocyte necrosis in female rats was selected as the point of departure for the MRL because it is reasonably consistent with the observed findings. The intermediate-duration oral MRL of 0.5 mg/kg/day was derived by dividing the BMDL by a composite uncertainty factor of 100 (10 for extrapolation from humans and 10 for human variability).

No chronic-duration oral MRL has been derived for 1,1,2,2-tetrachloroethane due to insufficient data. Information on the chronic oral toxicity of 1,1,2,2-tetrachloroethane is limited to a 78-week carcinogenicity bioassay in rats and mice that were exposed by gavage (NCI 1978). Interpretation of the rat study is confounded by high incidences of endemic chronic murine pneumonia, although this is unlikely to have contributed to effects observed in the liver; based on an increased incidence of hepatic fatty changes, a NOAEL of 62 mg/kg/day and LOAEL of 108 mg/kg/day were identified in the rats. The mouse study identified a serious LOAEL of 284 mg/kg/day for reduced survival and lethal kidney lesions (acute toxic tubular nephrosis), but high incidences of hepatocellular tumors in all exposed groups (142 and 284 mg/kg/day) precluded evaluation of noncancer effects in the liver and identification of a NOAEL or less-serious LOAEL in the mice. No chronic oral MRL was derived because lower LOAELs were identified in the more comprehensive and sensitive 14-week dietary study (NTP 2004a) used to derive the intermediate-duration MRL.

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3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of 1,1,2,2-tetrachloroethane. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between

"less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of 1,1,2,2-tetrachloroethane are indicated in Table 3-2 and Figure 3-2. Because cancer effects could occur at lower exposure levels, Figure 3-2 also shows a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 (10-4 to 10-7), as developed by EPA.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

As discussed below, the database on health effects of 1,1,2,2-tetrachloroethane is limited by a paucity of studies in humans. The information in humans is generally very dated, incomplete, and unsuitable for determination of reliable effect levels.

3.2.1 Inhalation Exposure

3.2.1.1 Death

A few human deaths have been reported following excessive inhalation exposure to 1,1,2,2-tetrachloroethane. Immediately after World War I, gastrointestinal and neurological distress were reported following occupational exposure to a varnish containing 1,1,2,2-tetrachloroethane that was used to cover fabric airplane wings. Although workers generally recovered, at least 4 of 14 workers later became confused, delirious, comatose, and finally died (Willcox et al. 1915). Autopsies revealed extreme liver

destruction and fatty degeneration of the liver. The levels of 1,1,2,2-tetrachloroethane in the air were not measured, so inhaled concentrations that may cause death in humans are not known.

Inhalation of 1,1,2,2-tetrachloroethane has also been shown to cause death in animals. Mortality resulted from exposure to concentrations of 1,000–1,253 ppm for 4–6 hours in rats (Carpenter et al. 1949; Deguchi 1972; Schmidt et al. 1980b; Smyth et al. 1969), 1,168–5,900 ppm for 1.5–3 hours in mice (Horiuchi et al. 1962; Pantelitsch 1933), and 5,050–6,310 ppm for 30 minutes in rats and guinea pigs (NIOSH 1978). Mortality was reported in rats and mice repeatedly exposed to 1,1,2,2-tetrachloroethane vapors (Horiuchi et al. 1962). For example, exposure of six male rats at a concentration of 9,000 ppm (2 hours/day, once/week for a total of five exposures) resulted in 100% mortality; three of the six rats died following the first exposure period. All nine male mice exposed to 1,1,2,2-tetrachloroethane vapors at a concentration of 7,000 ppm for 2 hours once a week died during a 29-day study. All exposures from reliable studies that caused death in rats, mice, and guinea pigs are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.2 Systemic Effects

No studies were located regarding musculoskeletal or dermal effects in humans or animals following inhalation exposure to 1,1,2,2-tetrachloroethane. The systemic effects observed in humans and animals after inhalation exposure to 1,1,2,2-tetrachloroethane are discussed below. The highest NOAEL and all LOAEL values from each reliable study for systemic end points in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

Respiratory Effects. Minor effects on the respiratory system are caused by 1,1,2,2-tetrachloroethane in humans. At a concentration of 13 ppm, but not 2.9 ppm, mucosal irritation occurred in two humans exposed for 10–30 minutes. Odor was noticed at the lowest concentration tested (2.9 ppm) (Lehmann and Schmidt-Kehl 1936).

Labored respiration was observed in rats and guinea pigs exposed to 1,1,2,2-tetrachloroethane vapors at lethal concentrations (5,050 or 6,310 ppm) for 30 minutes; histological examinations showed no treatment-related lesions in the lungs (NIOSH 1978). There was no histopathological evidence of exposure-related effects on the respiratory system of a monkey exposed to a time-weighted average (TWA) concentration of 1,974 ppm for 2 hours/day, 6 days/week for 9 months (Horiuchi et al. 1962), although the monkey study is limited by only one test animal and no control.

Table 3-1 Levels of Significant Exposure to 1,1,2,2-Tetrachloroethane - Inhalation

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (Sherman)	4 hr				1000 (2/6 died)	Carpenter et al. 1949	
2	Rat (Sprague-Dawley)	30 min				5050 (3/10 died)	NIOSH 1978	
3	Rat (Wistar)	4 hr				1253 M (LC50)	Schmidt et al. 1980b	
4	Mouse (NS)	3 hr				5900 M (3/10 died)	Horiuchi et al. 1962	
5	Mouse (NS)	1.5-2 hr				1168 (3/3 died)	Pantelitsch 1933	
6	Gn Pig (Hartley)	30 min				6310 (3/10 died)	NIOSH 1978	

Table 3-1 Levels of Significant Exposure to 1,1,2,2-Tetrachloroethane - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
Systemic								
7	Rat (Sprague-Dawley)	30 min	Resp	576		5050 (labored respiration)	NIOSH 1978	Labored respiration occurred at lethal exposure levels.
			Cardio	6310				
			Hepatic	6310				
			Renal	6310				
			Endocr	6310				
			Ocular	576	5050 (lacrimation)			
			Bd Wt	6310				
8	Mouse (NS)	3 hr	Hepatic		5900 M (congestion and fatty degeneration of the liver)		Horiuchi et al. 1962	
9	Mouse (Cb)	3 hr	Hepatic		600 F (increased triglycerides and total lipids and decreased ATP in liver)		Tomokuni 1969	
10	Mouse (Cb)	3 hr	Hepatic		800 F (increased triglycerides and decreased phospholipids in liver)		Tomokuni 1970	

Table 3-1 Levels of Significant Exposure to 1,1,2,2-Tetrachloroethane - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)		LOAEL Serious (ppm)		Reference Chemical Form	Comments
11	Gn Pig (Hartley)	30 min	Resp	576			5050	(labored respiration)	NIOSH 1978	Labored respiration occurred at lethal exposure levels.
			Cardio	6310						
			Hepatic	6310						
			Renal	6310						
			Endocr	6310						
			Ocular		576	(lacrimation, squinting, eye closure)				
			Bd Wt	6310						
Neurological										
12	Rat (NS)	6 hr					360	(50% decreased motor activity)	Horvath and Frantik 1973	
13	Rat (Sprague-Dawley)	30 min			576	(reduced activity and alertness)	5050	(narcosis)	NIOSH 1978	
14	Mouse (NS)	1.5-2 hr					1022	(prostration, loss of reflexes)	Pantelitsch 1933	
15	Gn Pig (Hartley)	30 min			576	(reduced activity)	5050	(narcosis and tremors)	NIOSH 1978	

Table 3-1 Levels of Significant Exposure to 1,1,2,2-Tetrachloroethane - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
INTERMEDIATE EXPOSURE								
Death								
16	Rat (NS)	29 d 2-3 d/wk 2 hr/d				9000 M (6/6 died)	Horiuchi et al. 1962	3/6 Deaths occurred prior to the second exposure period.
17	Mouse (NS)	29 d 1 d/wk 2 h/d				7000 M (9/9 died)	Horiuchi et al. 1962	5/9 Deaths occurred within 5 days following the first exposure period.
Systemic								
18	Monkey (Macaca cynomolga)	9 mo 6 d/wk 2 hr/d	Hepatic		1974 M (fatty degeneration)		Horiuchi et al. 1962	
19	Rat (NS)	29 d 2-3 d/wk 2 hr/d	Hemato		9000 M (decreases red cell count and hemoglobin content)		Horiuchi et al. 1962	
			Hepatic		9000 M (congestion and fatty degeneration)			
			Bd Wt	9000 M				
20	Mouse (NS)	29 d 1 d/wk 2 h/d	Hepatic		7000 M (congestion and fatty degeneration)		Horiuchi et al. 1962	
Neurological								
21	Monkey (Macaca cynomolga)	9 mo 6 d/wk 2 hr/d				1974 M (near unconsciousness)	Horiuchi et al. 1962	Near unconsciousness noted as early as the 15th exposure period.

Table 3-1 Levels of Significant Exposure to 1,1,2,2-Tetrachloroethane - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
22	Rat (NS)	29 d 2-3 d/wk 2 hr/d				9000 M (ataxia and loss of consciousness)	Horiuchi et al. 1962	
Reproductive								
23	Rat (NS)	9 mo 4 hr/d		1.9 M			Schmidt et al. 1972	Reproductive endpoints were adequately reported.

a The number corresponds to entries in Figure 3-1.

ATP = adenosine tri-phosphate; Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = Female; Gastro = gastrointestinal; Gn pig = guinea pig; Hemato = hematological; hr = hour(s); Immuno = immunological; LC50 = lethal concentration, 50% kill, LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); mo = month(s); NOAEL = no-observed-adverse-effect level; NS = not specified; occup = occupational; Resp = respiratory; wk = week(s)

Figure 3-1 Levels of Significant Exposure to 1,1,2,2-Tetrachloroethane - Inhalation

Acute (≤14 days)

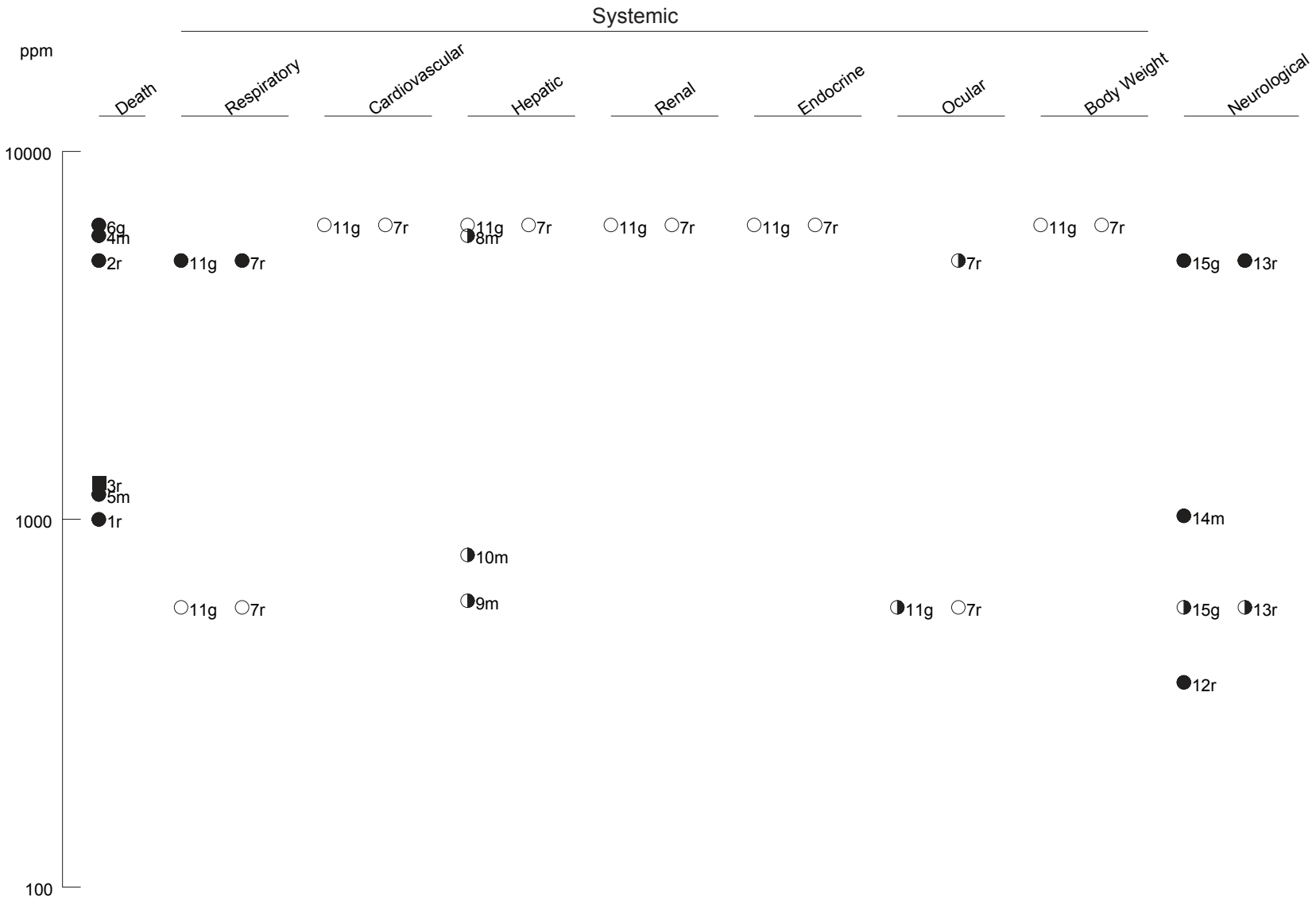
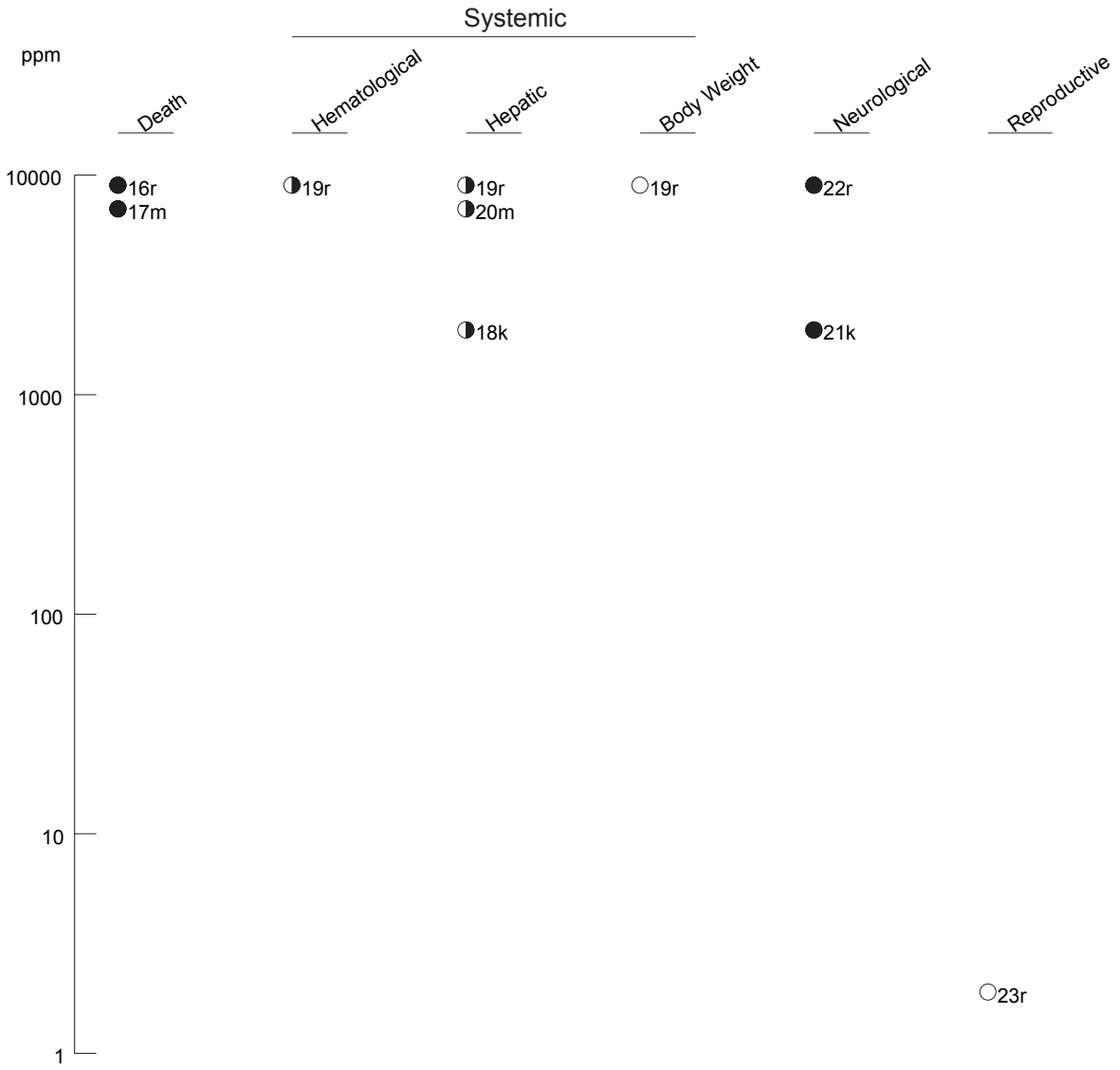


Figure 3-1 Levels of Significant Exposure to 1,1,2,2-Tetrachloroethane - Inhalation *(Continued)*

Intermediate (15-364 days)



c-Cat -Humans f-Ferret n-Mink
d-Dog k-Monkey j-Pigeon o-Other
r-Rat m-Mouse e-Gerbil
p-Pig h-Rabbit s-Hamster
q-Cow a-Sheep g-Guinea Pig

◆ Cancer Effect Level-Animals
● LOAEL, More Serious-Animals
◑ LOAEL, Less Serious-Animals
○ NOAEL - Animals

▼ Cancer Effect Level-Humans
▲ LOAEL, More Serious-Humans
◭ LOAEL, Less Serious-Humans
△ NOAEL - Humans

■ LD50/LC50
Minimal Risk Level for effects other than Cancer

Cardiovascular Effects. Humans exposed to 1,1,2,2-tetrachloroethane in factories showed few, if any, effects on the cardiovascular system. World War II army workers who were exposed to unknown levels of 1,1,2,2-tetrachloroethane during its use as a solvent in a clothing impregnation process showed no increase in deaths due to cardiovascular diseases in a 30-year follow-up period (Norman et al. 1981). When compared with cause-, age-, race-, and calendar year-specific U.S. mortality rates, the standard mortality ratio (SMR) for cardiovascular disease was 0.79 (confidence intervals not reported); additional information on this study is presented in Section 3.2.1.7. Workers exposed to 1,1,2,2-tetrachloroethane in a chemical plant in Italy showed no important clinical changes in cardiovascular function (Gobbato and Bobbio 1968). Exposure levels were not measured in either of these studies.

No pathological changes in rat hearts were found after a 6-hour exposure to 100 ppm (Deguchi 1972). Myocardial damage was found in 1 of 10 rats following exposure to 6,310 ppm for 30 minutes; no such effect occurred in a guinea pig subjected to this same exposure (NIOSH 1978).

No histopathological changes were seen in the heart of a monkey that was exposed to a TWA concentration of 1,974 ppm 1,1,2,2-tetrachloroethane for 2 hours/day, 6 days/week for 9 months (Horiuchi et al. 1962). However, only one monkey was studied, and a control was not included.

Gastrointestinal Effects. Humans exposed to 1,1,2,2-tetrachloroethane in the workplace often developed gastric distress including pain, nausea, vomiting, loss of appetite, and loss of body weight. Such symptoms were found in workers in the fabric airplane wing varnish industry in World War I (Coyer 1944; Willcox et al. 1915), in a penicillin factory in Czechoslovakia (Jeney et al. 1957), and in a jewelry factory in India (Lobo-Mendonca 1963). Although specific complaints were not associated with specific levels of exposure, the exposure levels in the facilities ranged from 1 to 248 ppm. The adverse health effects generally disappeared when the workers left their employment.

Two volunteers who inhaled 1,1,2,2-tetrachloroethane fumes for 10–30 minutes experienced nausea and vomiting after exposure to 2.9 ppm for 20 minutes (Lehmann and Schmidt-Kehl 1936).

Data regarding gastrointestinal effects in animals following inhalation exposure to 1,1,2,2-tetrachloroethane are limited. One monkey exposed to 1,974 ppm for 2 hours/day, 6 days/week for 9 months had diarrhea and anorexia between the twelfth and fifteenth exposures and subsequently recovered (Horiuchi et al. 1962). However, no control monkey was included.

Hematological Effects. An increase in the number of large mononuclear cells, white blood cells, and platelets, and slight anemia, were found in workers in an artificial silk factory who were exposed to 1,1,2,2-tetrachloroethane vapors (Minot and Smith 1921). 1,1,2,2-Tetrachloroethane levels were not accurately measured.

Two of three male rats that were intermittently exposed to 9,000 ppm for 29 days showed decreases in red blood cells and hemoglobin content (Horiuchi et al. 1962). A monkey exposed to 1,974 ppm intermittently for 9 months showed sporadic changes in hematocrit, red blood cell, and white blood cell counts, but these changes showed no clear trend and only one animal was tested (Horiuchi et al. 1962).

Hepatic Effects. One of the most significant systemic effects of 1,1,2,2-tetrachloroethane is on the liver. Some humans exposed to 1,1,2,2-tetrachloroethane vapors in the workplace have developed jaundice and an enlarged liver (Coyer 1944; Horiuchi et al. 1962; Jeney et al. 1957; Koelsch 1915; Willcox et al. 1915). Specific clinical signs were not associated with specific exposure levels. Vapor concentrations were reported in one study to range from 1.5 to 248 ppm (Jeney et al. 1957).

Liver degeneration, as evidenced by liver congestion and necrosis, was observed in the autopsies of two humans who died after exposure to 1,1,2,2-tetrachloroethane (Willcox et al. 1915). World War II army workers who were exposed to unknown levels of 1,1,2,2-tetrachloroethane during its use as a solvent in a clothing impregnation process showed no increase in deaths due to cirrhosis of the liver in a 30-year follow-up period (Norman et al. 1981). When compared with cause-, age-, race-, and calendar year-specific U.S. mortality rates, the SMR for liver cirrhosis was 0.48 (confidence intervals not reported). Additional information on this study is presented in Section 3.2.1.7.

The liver is also the major target organ for 1,1,2,2-tetrachloroethane toxicity in animals. Fine droplet fatty degeneration of the liver was observed in rats following a single exposure to 60 ppm for 4 hours or exposure to 2 ppm for 4 hours/day for 8 of 10 days, but there were no clear changes in serum or liver chemistry indices at these exposure levels (Gohlke and Schmidt 1972; Schmidt et al. 1972). This histological alteration appeared to be mild and was accompanied by clear or suggestive increases in hepatic ascorbic acid and serum glutamate dehydrogenase and decreases in serum triglycerides at 102 ppm, increases in serum triglycerides and hexobarbital sleep time at 307 ppm, and increases in serum alanine aminotransferase and leukin aminopeptidase at 613 ppm (Schmidt et al. 1972), suggesting that 102 ppm was a minimal LOAEL for acute hepatic effects. No treatment-related histological effects were

found in the liver of rats or guinea pigs exposed to 6,310 ppm of 1,1,2,2-tetrachloroethane for 30 minutes (NIOSH 1978), although rats that were exposed to 9,000 ppm for 2 hours/day, 2 days/week for 4 weeks showed fatty livers (Horiuchi et al. 1962). Hepatic lipids and triglycerides were increased in mice exposed to 600–800 ppm for 3 hours (Tomokuni 1969, 1970), and fatty degeneration of the liver occurred in mice exposed to a lethal concentration of 5,900 ppm for 3 hours (Horiuchi et al. 1962). Rabbits that were exposed to 15 ppm for 7–11 months showed early signs of liver degeneration at necropsy (Navrotskiy et al. 1971). A single monkey exposed to a TWA concentration of 1,974 ppm of 1,1,2,2-tetrachloroethane for 2 hours/day, 6 days/week for 9 months also showed fatty degeneration of the liver (Horiuchi et al. 1962).

Additional information on liver effects following intermediate-duration exposure to 1,1,2,2-tetrachloroethane is available from poorly reported studies that cannot be used to identify reliable effect levels. For example, Truffert et al. (1977) reported unquantified increases in relative liver weights and histopathological liver alterations in female rats exposed to 1,1,2,2-tetrachloroethane vapors at a reported concentration of 560 mL/m^3, for 5 or 6 hours/day, 5 days/week for up to 15 weeks. The histological liver alterations were observed after nine exposures and included granular appearance, cytoplasmic vacuolization, and evidence of hyperplasia (increase in number of binuclear cells and appearance of mitosis), but the alterations regressed after 19 exposures and were no longer observed after 39 exposures. Incidences and severity of the liver lesions were not reported. Reliable effect levels cannot be established for this study due to the lack of information regarding incidence and severity of effects and exposure-response (due to the use of a single exposure level), as well as uncertainty regarding the actual exposure concentration. If it is assumed that mL/m^3 is a volume/volume vapor concentration, then the reported concentration is equivalent to 560 ppm. If it is assumed that 560 mL is the volume of liquid volatilized in 1 m^3 of air, then the reported concentration is equivalent to 130,325 ppm, a level over 100 times higher than the acute LC_{50}.

Renal Effects. No recent studies were located regarding renal effects in humans following inhalation exposure to 1,1,2,2-tetrachloroethane. Fatty degeneration and congestion of the kidney were found in one female who had died following inhalation of 1,1,2,2-tetrachloroethane over a 2–3-month period (Willcox et al. 1915), but exposure concentrations were not defined.

No treatment-related histological effects were found in the kidneys of rats or guinea pigs exposed to 6,310 ppm for 30 minutes (NIOSH 1978), rats exposed to 613 ppm for 4 hours (Schmidt et al. 1972), or rats exposed to 2 ppm for 4 hours/day for 8 of 10 days (Gohlke and Schmidt 1972). Similarly, no

treatment-related histopathological lesions in the kidney were found in one monkey exposed to a TWA concentration of 1,974 ppm for 2 hours/day, 6 days/week for 9 months (Horiuchi et al. 1962), although this study is limited by the use of a single animal.

Endocrine Effects. No studies were located regarding endocrine effects in humans following inhalation exposure to 1,1,2,2-tetrachloroethane.

No treatment-related histological effects were found in the adrenals of rats or guinea pigs exposed to 6,310 ppm for 30 minutes (NIOSH 1978) or pancreas of one monkey exposed to a TWA concentration of 1,974 ppm for 2 hours/day, 6 days/week for 9 months (Horiuchi et al. 1962). There were no changes in thyroid histology, morphometry (diameter and number of follicles and epithelial nuclei, height of follicular epithelium), or absorption of injected ^{131}I in rats exposed to 2 ppm for 4 hours/day for 8 of 10 days (Gohlke and Schmidt 1972).

Ocular Effects. Humans exposed to 1,1,2,2-tetrachloroethane vapors (130 ppm) for 10 minutes experienced ocular mucosal irritation (Lehmann and Schmidt-Kehl 1936). Similarly, guinea pigs exposed to 576 ppm for 5 minutes exhibited eye closure and squinting; by 15 minutes, lacrimation was common (NIOSH 1978). Rats showed these effects at 5,050 ppm. These ocular effects are due to direct contact of the eyes with the vapors, rather than a true systemic effect due to inhalation of the vapor.

Body Weight Effects. Humans exposed to 1,1,2,2-tetrachloroethane vapors in an occupational setting experienced a 5–15-pound weight loss (Parmenter 1921). However, this weight loss was probably attributable to gastrointestinal disturbances (i.e., nausea, diarrhea, and vomiting) (Parmenter 1921).

No effects on body weight were found in several inhalation studies in animals (Horiuchi et al. 1962; NIOSH 1978; Schmidt et al. 1972, 1980b).

3.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological or lymphoreticular effects in humans following inhalation exposure to 1,1,2,2-tetrachloroethane.

Rabbits were exposed 0, 0.3, 1.5, or 14.6 ppm of 1,1,2,2-tetrachloroethane for 3 hours/day, 6 days/week for 8–10 months (Shmuter 1977). Animals were vaccinated with typhoid vaccine 1.5, 4.5–5, and 7.5–

8 months after the initiation of 1,1,2,2-tetrachloroethane exposure. Significant increases and decreases in total antibody levels were observed in the 0.3 and 14.6 ppm groups, respectively. No significant changes in 7S-typhoid antibody levels were observed. Significant alterations in the levels of "normal hemolysins to the Forssmann antigen of sheep erythrocytes" were observed in the 1.5 and 14.6 ppm groups; levels were increased at 1.5 ppm after 1.5, 2, and 2.5 months of exposure and decreased after 4 months of exposure, and decreased at 14.6 ppm[3] during the first 6 months of exposure. Increases in the electrophoretic mobility of specific antibodies were also reported. Exposure to 14.6 ppm resulted in a decrease in the relative content of antibodies in the γ globulin fraction and an increase in the α and β fractions. This is a poorly reported study that provides inadequate quantitative data. The reporting limitations, end points of uncertain toxicological significance, and inconsistent patterns of response preclude assessing biological significance and identification of a NOAEL or LOAEL. No histopathological changes were noted in the spleens of rats that inhaled 100 ppm 1,1,2,2-tetrachloroethane for 6 hours (Deguchi 1972). The significance of this finding is unclear due to a lack of immune function tests.

3.2.1.4 Neurological Effects

Volunteers who inhaled 1,1,2,2-tetrachloroethane (116 ppm and higher for 10–30 minutes) reported being dizzy. These effects did not occur when the exposure was 13 ppm (Lehmann and Schmidt-Kehl 1936). Humans exposed to 1,1,2,2-tetrachloroethane fumes in the workplace showed symptoms such as headache, tremors, dizziness, numbness, and drowsiness (Hamilton 1917; Jeney et al. 1957; Lobo-Mendonca 1963; Minot and Smith 1921; Parmenter 1921). Length of exposure was not specifically noted, but the reports seem to indicate that the exposures were generally for a period of about 18 months or less. Exposure levels were only noted in one study, and these ranged from 9 to 98 ppm, with significant skin exposure in addition to the inhalation exposure (Lobo-Mendonca 1963).

In acute-duration experiments, rats showed a 50% decrease in spontaneous motor activity after being exposed to 360 ppm for 6 hours (Horvath and Frantik 1973). As the concentration of, or duration of exposure to, 1,1,2,2-tetrachloroethane increased, mice, rats, and guinea pigs showed some combination of a loss of reflexes, loss of spontaneous motor activity, ataxia, prostration, and narcosis (Lazarew 1929; Pantelitsch 1933; NIOSH 1978). Rats and guinea pigs that were exposed for 30 minutes had reduced activity at 576 ppm and narcosis at 5,050 ppm (NIOSH 1978), and mice showed prostration and loss of reflexes after being exposed to 1,022–1,091 ppm for 2 hours (Lazarew 1929; Pantelitsch 1933). Narcosis was observed in a cat exposed to 8,300 ppm for 5 hours (Lehmann 1911). Rats exposed to 9,000 ppm for

2 hours/day, twice a day for 4 weeks exhibited hyperactivity, ataxia, and then unconsciousness (Horiuchi et al. 1962). One monkey exposed to a TWA of 1,974 ppm of 1,1,2,2-tetrachloroethane for 2 hours/day, 6 days/week for 9 months exhibited unconsciousness after each 2-hour exposure, starting at the 15th exposure (Horiuchi et al. 1962).

The highest NOAEL and all LOAEL values from each reliable study for neurological end points in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans following inhalation exposure to 1,1,2,2-tetrachloroethane.

Male rats were exposed to 0 or 2.2 ppm of 1,1,2,2-tetrachloroethane 4 hours/day for up to 8 days in a 10-day period (Gohlke and Schmidt 1972; Schmidt et al. 1972). Reproductive function was not tested, but evaluations included histological examinations of the testes in groups of seven control and seven treated males following the second, fourth, and eighth exposures. This study is limited by imprecise and incomplete reporting of results. It was noted that testicular histopathology, described as atrophy of the seminal tubules with strongly restricted or absent spermatogenesis, was observed in five exposed animals following the fourth exposure; data for the other time periods and the control group were not reported. The biological significance of the testicular histological changes is unclear because these changes apparently were not observed at the end of the study, and there were no effects on reproductive function in male rats that were chronically exposed to a similar concentration of 1,1,2,2-tetrachloroethane (1.9 ppm) (Schmidt et al. 1972).

Male rats were exposed to 0 or 1.9 ppm of 1,1,2,2-tetrachloroethane 4 hours/day for 265 days. One week before the end of the exposure period, each of 7 control and 7 exposed males was mated with 5 unexposed virgin females, yielding corresponding groups of 35 mated females. The offspring were observed for 84 days and were examined macroscopically for malformations. Other reported study end points were percentage of mated females having offspring, littering interval, time to 50% littered, total number of pups, pups per litter, average birth weight, postnatal survival on days 1, 2, 7, 14, 21, and 84, and sex ratio and average body weight on postnatal day 84. No macroscopic malformations or significant group differences in the other indices were found, indicating that 1.9 ppm was a NOAEL for male reproductive toxicity in rats.

Rats and guinea pigs that were exposed to 6,310 ppm (43,350 mg/m^3) 1,1,2,2-tetrachloroethane for 30 minutes had no exposure-related organ weight or gross or histological changes in the testes, epididymides, ovaries, or uterus when examined 14 days post-exposure (NIOSH 1978). There were no histopathological changes in the testes of one monkey that was exposed to a TWA concentration of 1,974 ppm for 2 hours/day, 6 days/week for 9 months (Horiuchi et al. 1962). Lack of histopathology, however, does not necessarily indicate that these male and female animals could produce appropriate numbers of healthy offspring. Since no mating studies with rats, guinea pigs, or monkeys exposed to high levels of 1,1,2,2-tetrachloroethane vapors have been conducted, no reproductive effect levels are indicated in Table 3-1 or Figure 3-1.

3.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans following inhalation exposure to 1,1,2,2-tetrachloroethane.

The potential for 1,1,2,2-tetrachloroethane-induced developmental effects in animals was assessed in a study that included inhalation exposure of male rats to 1.9 ppm 1,1,2,2-tetrachloroethane 4 hours/day, for an unspecified number of times during a 9-month period (Schmidt et al. 1972). One week before the end of the exposure period, exposed males and control males were mated with unexposed females and the F_1 generation was observed for 12 weeks. There was no effect on the number of offspring per litter, neonatal body weight, viability of the offspring, sex ratios, and body weight on day 84. No gross malformations were observed in the offspring.

3.2.1.7 Cancer

Mortality experience was evaluated in 1,099 white male World War II army workers who were exposed to 1,1,2,2-tetrachloroethane in 10 plants during its use as a solvent for impregnating clothing with N-dichloro-hexachloro-diphenyl-urea as a protectant against mustard gas (Norman et al. 1981). Exposure could have included the dermal route and was not measured, estimated, or documented on a man-for-man basis, but wasbased on job category (processing, laundry, or dry cleaning duties). Information from seven of the companies indicated that exposure to the solvent ranged from 5 weeks to 1 year (average approximately 5 months), and the workers were followed for 31 years. When compared with cause-,

age-, race-, and calendar year-specific U.S. mortality rates, the SMR for all malignancies was 0.96 (confidence intervals not reported). When the exposed group was compared with 1,319 workers in 29 other plants that used a water suspension instead of 1,1,2,2-tetrachloroethane in the impregnating process, there were slight increases for mortality from leukemia and aleukemia (relative risk [RR]=2.72, 90% confidence interval [CI] 0.96–7.70) and cancer of the genital organs (RR=1.58, 90% CI 0.58–4.83). This comparison showed no increases for the following cancer sites: all malignancies, buccal cavity and pharynx, digestive organs and peritoneum, respiratory system, urinary organs, and other lymphatic. Since the numbers of deaths were small (four from leukemia and aleukemia and three from gential organ cancers in the solvent-exposed group), the increases in risk were small, no significant excesses were found, and other confounding factors may have been present (i.e., exposure to other chemicals and a lack of occupational histories following exposure), the authors concluded that the results are difficult to interpret and the observed increases in cancer mortality may not have been due to 1,1,2,2-tetrachloroethane exposure. This information is inconclusive as to whether 1,1,2,2-tetrachloroethane causes cancer in humans.

No other studies were located regarding carcinogenicity in animals following inhalation exposure to 1,1,2,2-tetrachloroethane.

3.2.2 Oral Exposure

3.2.2.1 Death

A number of human suicides from drinking 1,1,2,2-tetrachloroethane have been reported. In reports of intentional ingestion of lethal amounts of 1,1,2,2-tetrachloroethane (Elliott 1933; Forbes 1943; Hepple 1927; Lilliman 1949; Mant 1953; Sherman 1953), subjects usually lost consciousness within approximately 1 hour and died 3–20 hours postingestion, depending on the amount of food in the stomach. Postmortem examinations showed gross congestion in the esophagus, stomach, kidneys, spleen, and trachea, gross congestion and edema in the lungs, and histological effects of congestion and cloudy swelling in the lungs, liver, and/or kidneys (Hepple 1927; Mant 1953). Amounts of 1,1,2,2-tetrachloroethane recovered from the stomach and intestines of these deceased subjects included 12 mL (Hepple 1927), 25 g (Lilliman 1949), 48.5 mL (Mant 1953), and 425 mL (Mant 1953). Assuming a density of 1.594 g/mL and an average body weight of 70 kg, the approximate minimum doses ingested in these cases are estimated to be approximately 273, 357, 1,100, and 9,700 mg/kg, respectively, although the actual doses are likely higher because the estimates are based on amounts of chemical recovered from the

gastrointestinal tract. No deaths occurred in eight patients (six males and two females) who were accidentally given 3 mL (68 mg/kg, using the above assumptions), or three patients (one young man, one young woman, one 12-year-old girl) accidentally administered 2 or 3 mL (98–118 mg/kg, using the assumed density and reported body weights), as medicinal treatment for hookworm (Sherman 1953; Ward 1955).

Mortality following oral exposure to 1,1,2,2-tetrachloroethane has been assessed in rats and mice. Single dose gavage LD_{50} values in rats range from 250 to 800 mg/kg (Gohlke et al. 1977; NTP 2004a; Schmidt et al. 1980a; Smyth et al. 1969). Gavage exposure to 540 mg/kg/day for 3–5 days (NTP 1993a, 1993b), 300 mg/kg/day for 3 days (Hanley et al. 1988), or 208 mg/kg/day for 13–21 days (NTP 1996) also caused mortality in rats. In mice, a gavage dose of 1,350 mg/kg/day for 3 days was lethal (NTP 1993d). Dietary exposure caused moribundity or death in rats at 558 mg/kg/day for 11 days (NTP 2004a), pregnant mice at 2,120 mg/kg/day for 14 days (NTP 1991b), and mice at 2,394 mg/kg/day for 6 days (NTP 1993c, 2004). NCI (1978) performed 6-week range-finding gavage studies that appear to have used mortality and body weight as the only end points to assess toxicity. The 316 mg/kg treatment level resulted in reported mortality in rats, but not mice. There was no treatment-related mortality in rats or mice administered 1,1,2,2-tetrachloroethane in the diet for 14 weeks at concentrations resulting in reported daily doses as high as 320 and 1,400 mg/kg/day, respectively (NTP 2004a).

Significantly decreased survival was observed in male and female mice administered 1,1,2,2-tetrachloroethane via oral gavage for 78 weeks at a reported TWA dose of 284 mg/kg/day (NCI 1978). Male and female rats were also administered 1,1,2,2-tetrachloroethane at TWA doses of 62 and 108 mg/kg/day (males) and 43 and 76 mg/kg/day (females) for 78 weeks (NCI 1978). Reduced survival was reported in the high-dose female rats, but survival in the female rats may have been influenced by high incidences of chronic murine pneumonia in controls and treatment groups alike; there was no apparent effect on survival in the male rats.

All reliable LOAEL values from each reliable study for death in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.2 Systemic Effects

No studies were located regarding musculoskeletal effects in humans or animals following oral exposure to 1,1,2,2-tetrachloroethane. The highest NOAEL and all LOAEL values from each reliable study for

Table 3-2 Levels of Significant Exposure to 1,1,2,2-Tetrachloroethane - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Human	once (IN)				273 M (death)	Hepple 1927	
2	Human	once (IN)				357 (death)	Lilliman 1949	
3	Human	once (IN)				1100 M (death)	Mant 1953	
4	Human	once (IN)				9700 M (death)	Mant 1953	
5	Rat (Osborne-Mendel)	3 d 1 x/d (GO)				300 M (1/5 died)	Dow 1988	
6	Rat (NS)	once (GO)				250 M (LD50)	Gohlke et al. 1977	
7	Rat (Fischer- 344)	3 d 1 x/d (GO)				540 M (5/5 males died)	NTP 1993a	
8	Rat (Fischer- 344)	3-5 d 1 x/d (GO)				540 (5/5 males and 5/5 females died)	NTP 1993b	
9	Rat (Fischer- 344)	13-14 d 7 d/wk 1 x/d (GO)				208 M (5/5 moribund or dead)	NTP 1996	

Table 3-2 Levels of Significant Exposure to 1,1,2,2-Tetrachloroethane - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
10	Rat (Fischer- 344)	11 d ad lib (F)				558 F (moribund)	NTP 2004a	
11	Rat (NS)	once (G)				800 (LD50)	NTP 2004a	
12	Rat (Wistar-C)	once (GO)				330 M (LD50)	Schmidt et al. 1980a	
13	Rat (Carnworth-Wistar)	once (G)				319 M (LD50)	Smyth et al. 1969	
14	Mouse (CD-1)	11 d Gd 6-16 ad lib (F)				2120 F (2/10 maternal deaths)	NTP 1991b	
15	Mouse (B6C3F1)	3 d 1 x/d (GO)				1350 (5/5 males and 5/5 females moribund or dead)	NTP 1993d	
16	Mouse (B6C3F1)	6 d ad lib (F)				2394 M (2/5 died)	NTP 2004a	
Systemic								
17	Human	once (IN)	Gastro	357	(congestion of stomach lining)		Lilliman 1949	
			Hepatic	357	(slight liver congestion)			

Table 3-2 Levels of Significant Exposure to 1,1,2,2-Tetrachloroethane - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
18	Human	once (IN)	Resp			9600 M (lung collapse)	Mant 1953	
			Gastro		9600 M (congestion of esophagus and stomach)			
19	Human	once (IN)	Resp			1100 M (extreme lung congestion and edema)	Mant 1953	
			Cardio			1100 M (epicardial and endocardinal anoxic petechial hemorrhage)		
			Gastro		1100 M (pronounced congestion of gastric mucosa)			
			Hepatic	1100 M				
			Renal	1100 M				
20	Rat (Sprague-Dawley)	once (GO)	Hepatic	287 M	574 M (increased serum AST and ALT)		Cottalasso et al. 1998	
21	Rat (Osborne-Mendel)	3 d 1 x/d (GO)	Hepatic	300 M			Dow 1988	
			Bd Wt	150 M	300 M (16% reduced body weight)			

Table 3-2 Levels of Significant Exposure to 1,1,2,2-Tetrachloroethane - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
22	Rat (Sprague-Dawley)	11d GD 6-16 ad lib (F)	Bd Wt	34 F			NTP 1991a	
23	Rat (Fischer- 344)	12 of 14 d 1 x/d (GO)	Bd Wt	135 M		270 M (55% reduced body weight gain)	NTP 1993a	
24	Rat (Fischer- 344)	12 of 14 d 1 x/d (GO)	Bd Wt	135	270 (17-22% decreased final body weight)		NTP 1993b	
25	Mouse (B6C3F1)	4 d 1 x/d (GO)	Hepatic	300 M			Dow 1988	
			Bd Wt	300 M				
26	Mouse (CD-1)	11 d Gd 6-16 ad lib (F)	Bd Wt		987 F (14% decreased maternal body weight gain during treatment)		NTP 1991b	
27	Mouse (B6C3F1)	6 d ad lib (F)	Hepatic		2394 (hepatocellular degeneration)		NTP 2004a	
Neurological								
28	Human	once (IN)				68 (unconsciousness and other signs of narcosis)	Sherman 1953	

Table 3-2 Levels of Significant Exposure to 1,1,2,2-Tetrachloroethane - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
29	Human	once (IN)				98 (unconsciousness and other signs of narcosis)	Ward 1955	
30	Rat (Osborne-Mendel)	3-4 d 1 x/d (GO)				300 M (CNS depression and debilitation)	Dow 1988	
31	Rat (Fischer- 344)	12 of 14 d 1 x/d (GO)		135 M		270 M (lethargy)	NTP 1993a	
32	Rat (Fischer- 344)	1 d (GO)		135		270 (lethargy)	NTP 1993b	
33	Rat (Fischer- 344)	11 d ad lib (F)				591 M (lethargy) 558 F (lethargy)	NTP 2004a	
34	Rat (Wistar)	once (G)		25 F	50 F (increased electric shock perception threshold)	100 F (ataxia)	Wolff 1978	
35	Mouse (B6C3F1)	4 d 1 x/d (GO)		300 M			Dow 1988	
36	Mouse (B6C3F1)	4 d ad lib (F)				4788 M (lethargy)	NTP 2004a	

Table 3-2 Levels of Significant Exposure to 1,1,2,2-Tetrachloroethane - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Developmental								
37	Rat (Sprague-Dawley)	11d GD 6-16 ad lib (F)		98 F			NTP 1991a	
38	Mouse (CD-1)	11 d Gd 6-16 ad lib (F)		987 F			NTP 1991b	
INTERMEDIATE EXPOSURE								
Death								
39	Rat (Osborne-Mendel)	6 wk 5 d/wk (GO)				316 F (5/5 died)	NCI 1978	
Systemic								
40	Rat (Osborne-Mendel)	6 wk 5 d/wk (GO)	Bd Wt	100 M		178 M (38% reduced body weight gain)	NCI 1978	
				56 F		100 F (24% reduced body weight gain)		
41	Rat (Fischer- 344)	21 d 7 d/wk 1 x/d (GO)	Hepatic		104 M (increased liver weight, cytoplasmic vacuolation)		NTP 1996	
			Renal	104 M				
			Bd Wt	104 M				

Table 3-2 Levels of Significant Exposure to 1,1,2,2-Tetrachloroethane - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
42	Rat (Fischer- 344)	14 wk ad lib (F)	Resp	320			NTP 2004a	
			Cardio	320				
			Gastro	320				
			Hemato	320				
			Musc/skel	320				
			Hepatic	40[b]	80 (increased serum ALT and SDH, decreased serum cholesterol)			
			Renal	320				
			Endocr	320				
			Bd Wt	80		170 (29% reduced final body weight)		
43	Rat (Fischer- 344)	15 d ad lib (F)	Dermal	400 F	500 F (alopecia and acanthosis)		NTP 2004a	
			Bd Wt			300 (25-29% reduced final body weight)		
44	Mouse (B6C3F1)	6 wk 5 d/wk (GO)	Bd Wt	316			NCI 1978	

Table 3-2 Levels of Significant Exposure to 1,1,2,2-Tetrachloroethane - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
45	Mouse (B6C3F1)	12 of 16 d 1 x/d (GO)	Hepatic		337.5 F (hepatocellular degeneration)		NTP 1993d	
			Bd Wt	675				
46	Mouse (B6C3F1)	14 wk ad lib (F)	Cardio	1360			NTP 2004a	
			Gastro	1360				
			Musc/skel	1360				
			Hepatic	80 F	160 F (increased serum ALT, SDH and 5'-nucleotidase; decreased serum cholesterol)			
			Renal	1360				
			Endocr	1360				
			Bd Wt	200 M	370 M (12% reduced body weight gain)			
47	Mouse (B6C3F1)	15 d ad lib (F)	Hepatic		599 (hepatocellular degeneration)		NTP 2004a	
			Bd Wt		599 (10-14% reduced final body weight)			

Table 3-2 Levels of Significant Exposure to 1,1,2,2-Tetrachloroethane - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Neurological								
48	Rat (Fischer- 344)	21 d 7 d/wk 1 x/d (GO)		104 M		208 M (lethargy)	NTP 1996	
49	Rat (Fischer- 344)	14 wk ad lib (F)		80			NTP 2004a	Functional observational battery.
50	Mouse (B6C3F1)	12 of 16 d 1 x/d (GO)		337.5		675 (lethargy)	NTP 1993d	
51	Mouse (B6C3F1)	14 wk ad lib (F)		1360			NTP 2004a	
52	Mouse (B6C3F1)	15 d ad lib (F)			599 (hyperactivity)		NTP 2004a	
Reproductive								
53	Rat (Fischer- 344)	14 wk ad lib (F)		170 M 80 F		320 M (atrophy of prostate gland, seminal vesicle and testicular germinal epithelium) 170 F (uterine atrophy and changes in lengths of estrus cycle stages)	NTP 2004a	Atrophy of reproductive organs and tissues occurred at doses resulting in serious body weight effects in general.

Table 3-2 Levels of Significant Exposure to 1,1,2,2-Tetrachloroethane - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
54	Mouse (B6C3F1)	14 wk ad lib (F)		1360			NTP 2004a	
CHRONIC EXPOSURE								
Death								
55	Mouse (B6C3F1)	78 wk 5 d/wk (GO)				284 (reduced survival in both sexes; 55% in females)	NCI 1978	
Systemic								
56	Rat (Osborne-Mendel)	78 wk 5 d/wk (GO)	Cardio	108 M			NCI 1978	
			Gastro	108 M				
			Hepatic	62 M	108 M (fatty metamorphosis)			
			Renal	108 M				
			Endocr	108 M				
			Dermal	108 M				
			Bd Wt	62 M	108 M (18% depressed body weight)			
				43 F				
					76 F (14% depressed body weight)			

Table 3-2 Levels of Significant Exposure to 1,1,2,2-Tetrachloroethane - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
57	Mouse (B6C3F1)	78 wk 5 d/wk (GO)	Resp	284			NCI 1978	
			Cardio	284				
			Gastro	284				
			Hepatic	284				
			Renal	142		284 M (acute toxic tubular nephrosis)		
			Endocr	284				
			Dermal	284				
			Bd Wt	284				
Reproductive								
58	Rat (Osborne-Mendel)	78 wk 5 d/wk (GO)		108 M 76 F			NCI 1978	
59	Mouse (B6C3F1)	78 wk 5 d/wk (GO)		284			NCI 1978	

Table 3-2 Levels of Significant Exposure to 1,1,2,2-Tetrachloroethane - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)		Reference Chemical Form	Comments
Cancer									
60	Mouse (B6C3F1)	78 wk 5 d/wk (GO)				142	(CEL: hepatocellular carcinoma)	NCI 1978	

a The number corresponds to entries in Figure 3-2.

b Benchmark dose (BMD) analysis of the serum ALT data was used to calculate a benchmark dose limit (BMDL) of 26.6 mg/kg/day. An intermediate-duration oral minimal risk level (MRL) of 0.3 mg/kg/day was derived by dividing the BMDL by a composite uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

ad lib = ad libitum; ALT = alanine aminotransferase; AST = aspartate aminotransferase; Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; CNS = central nervous system; d = day(s); Endocr = endocrine; (F) = feed; F = Female; (G) = gavage; Gastro = gastrointestinal; gd = gestational day; (GO) = gavage in oil; Hemato = hematological; hr = hour(s); Immuno = immunological; (IN) = ingestion; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); mo = month(s); Metab = metabolic; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; occup = occupational; Resp = respiratory; SDH = sorbitol dehydrogenase; x = time(s); wk = week(s)

Figure 3-2 Levels of Significant Exposure to 1,1,2,2-Tetrachloroethane - Oral

Acute (≤14 days)

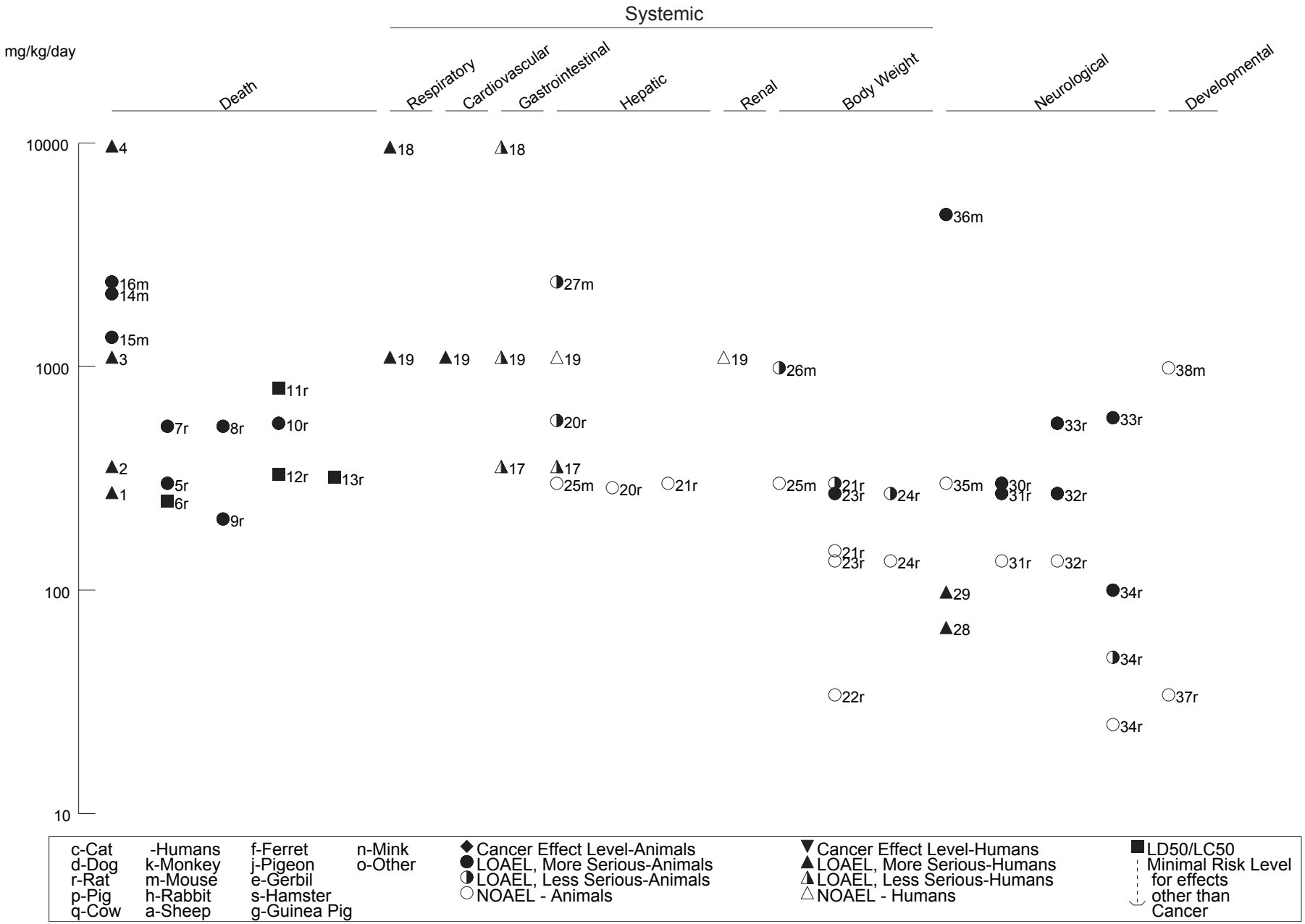


Figure 3-2 Levels of Significant Exposure to 1,1,2,2-Tetrachloroethane - Oral *(Continued)*

Intermediate (15-364 days)

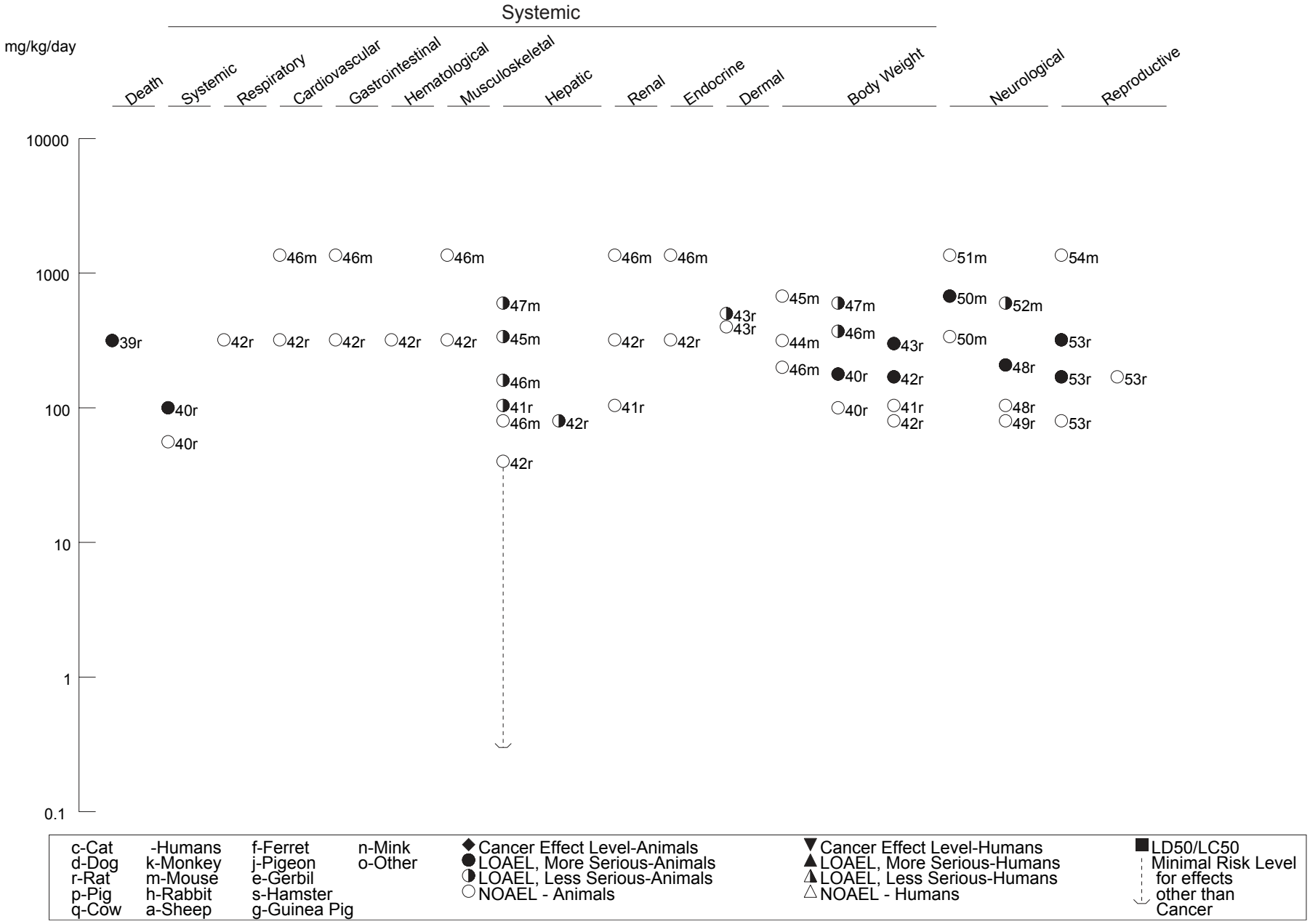
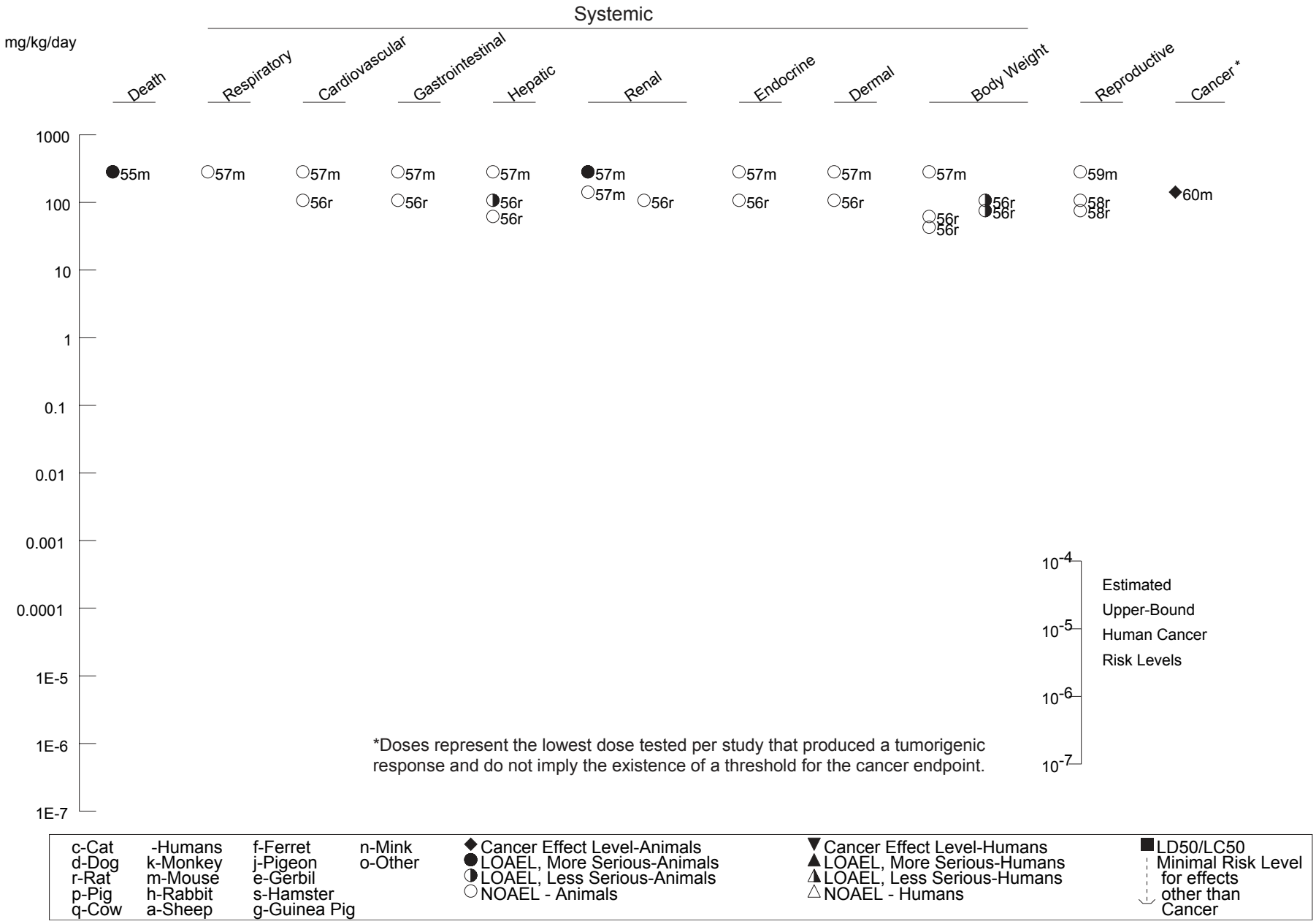


Figure 3-2 Levels of Significant Exposure to 1,1,2,2-Tetrachloroethane - Oral *(Continued)*

Chronic (≥365 days)



systemic end points in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

Respiratory Effects. Autopsy reports in humans following suicidal ingestion of at least 1,100 mg/kg of 1,1,2,2-tetrachloroethane revealed congestion and edema in the lungs (Hepple 1927; Mant 1953), but this did not appear to be the primary cause of death. A case of exposure at 9,600 mg/kg was reported to have caused lung collapse (Mant 1953). African men and women accidentally given oral doses of undiluted 1,1,2,2-tetrachloroethane (approximately 70–117 mg/kg) experienced shallow breathing during ensuing unconsciousness (Sherman 1953; Ward 1955).

Labored respiration, wheezing, and/or nasal discharge were observed in rats administered 1,1,2,2-tetrachloroethane in the diet for 78 weeks at reported TWA doses ranging from 43 to 108 mg/kg/day (NCI 1978). However, these effects may be at least partially attributable to the development of chronic murine pneumonia in controls and treatment groups alike. Mice treated for the same duration at concentrations resulting in daily 1,1,2,2-tetrachloroethane doses as high as 284 mg/kg/day experienced no respiratory effects (NCI 1978).

Cardiovascular Effects. African men and women accidentally given oral doses (approximately 70–117 mg/kg undiluted) experienced pronounced lowering of blood pressure (to 60/46) and faint pulse during ensuing unconsciousness (Sherman 1953; Ward 1955). A lethal oral dose (suicide) of 1,100 mg/kg produced epicardial and endocardial anoxic hemorrhage (Mant 1953).

Rats receiving up to 108 mg/kg/day and mice receiving 284 mg/kg/day orally for 78 weeks showed no gross or histological alterations of the heart (NCI 1978).

Gastrointestinal Effects. Single doses of 357 mg/kg or more caused mucosal congestion of the esophagus and upper stomach of humans (Lilliman 1949; Mant 1953). Rats receiving up to 108 mg/kg/day and mice receiving 284 mg/kg/day oral doses for 78 weeks showed no gross or microscopic histological alterations of the stomach, colon, pancreas, or bile duct (NCI 1978).

Hematological Effects. No information was located regarding 1,1,2,2-tetrachloroethane-induced hematological effects following oral exposure in humans. 1,1,2,2-Tetrachloroethane did not appear to cause hematological effects in male or female rats administered the chemical in the diet for 14 weeks at TWA doses as high as 320 mg/kg/day (NTP 2004a).

Hepatic Effects. Autopsy reports showed no evidence of damage to the livers of humans who ingested suicidal doses of 1,1,2,2-tetrachloroethane (Mant 1953). The lack of effect in the liver can be ascribed to the rapid lethality. In another autopsy report, slight congestion of the liver was reported from an accidental poisoning or suicide attempt with 1,1,2,2-tetrachloroethane (Lilliman 1949).

Rats administered a single gavage dose of 1,1,2,2-tetrachloroethane had toxicologically significant increases (>2-fold greater than controls) in serum AST at ≥574 mg/kg and serum ALT at 1,148 mg/kg (Cottalasso et al. 1998), but this study is limited by a lack of liver histology examinations; the NOAEL was 287 mg/kg. Hepatocellular degeneration occurred in mice exposed to a lethal dietary dose of 2,394 mg/kg/day for 6 days (NTP 2004a). Rats and mice that were exposed by gavage for 4 days had increased liver cell DNA synthesis (as shown by increased incorporation of [^{3}H]-thymidine) and increased mitotic activity at 75–300 mg/kg/day, but the only hepatic histological changes were centrilobular swelling and decreased periportal hepatocyte size in the mice at ≥75 mg/kg/day (Hanley et al. 1988). Because increased DNA synthesis and mitosis are not necessarily indicative of hepatotoxicity and the histological examinations showed no accompanying degenerative or other adverse liver lesions, this study identified a NOAEL of 300 mg/kg/day for hepatic effects. Rats that were exposed to a single 100 mg/kg gavage dose had no clearly adverse changes in serum ALT or other clinical chemistry indices, but the study was limited by inadequately reported liver histology data (Schmidt et al. 1980a). This study includes a general statement implying that the 100 mg/kg dose induced liver lesions, including necrosis and fatty degeneration, but the significance of the statement cannot be assessed because incidences and other specific histology data were not reported. These findings are not necessarily inconsistent with the lack of degenerative liver lesions in the rats exposed to gavage doses of 75–300 mg/kg/day for 4 days (Hanley et al. 1988), because 1,1,2,2-tetrachlorethane could have acted as a suicide substrate (see Section 3.4.3) in the single dose study (i.e., inactivated the metabolic enzymes needed to activate subsequent doses).

Hepatocellular degeneration was noted in mice exposed to 1,1,2,2-tetrachloroethane at levels of 599 mg/kg/day in the diet for 15 days (NTP 2004a) or 337.5 mg/kg/day by gavage for 16 days (NTP 1993d). Exposure to 104 mg/kg/day by gavage for 21 days caused mild to moderate hepatocellular cytoplasmic vacuolation in rats (NTP 1996), but no degenerative or other liver lesions. Hepatic effects in rats receiving 1,1,2,2-tetrachloroethane in the diet for 14 weeks included increases in hepatic cytoplasmic vacuolization at 20 mg/kg/day (lowest tested dose), liver weight at 40 mg/kg/day, and hepatocellular hypertrophy at 80 mg/kg/day (NTP 2004a). These hepatic effects are not considered adverse because the

severity of the vacuolation was minimal to mild and did not increase with dose, and the increases in liver weight and hepatocellular hypertrophy are considered adaptive responses to chemical exposure. Increases in serum ALT and SDH and decreases in serum cholesterol also occurred at ≥80 mg/kg/day, but the magnitudes of these changes were biologically significant only at 170 and 320 mg/kg/day. Other effects that occurred at 170 and 320 mg/kg/day included increases in serum ALP and bile acids, hepatocyte necrosis, bile duct hyperplasia, hepatocellular mitotic alterations, foci of cellular alterations, and liver pigmentation. This 14-week rat study (NTP 2004a) identified a NOAEL of 80 mg/kg/day and a LOAEL of 170 mg/kg/day based on adverse liver-related serum chemistry changes and histological manifestations of hepatocellular damage and was used as the basis for deriving an intermediate-duration oral MRL for 1,1,2,2-tetrachloroethane. NTP (2004a) similarly exposed mice to 1,1,2,2-tetrachloroethane in the diet for 14 weeks. Effects in the mice included minimal hepatocellular hypertrophy, increases in serum SDH, ALT, and bile acids, and decreased serum cholesterol at 160–200 mg/kg/day, but the magnitudes of these changes were biologically significant only at 300–370 mg/kg/day. Other effects that occurred in the mice at 300–370 mg/kg/day included increases in serum ALP and 5'-nucleotidase, necrosis, pigmentation, and bile duct hyperplasia. Based on the adverse serum chemistry and histopathological changes at 300 mg/kg/day and higher doses, this study identified a NOAEL of 200 mg/kg/day and a LOAEL of 300 mg/kg/day for liver toxicity in mice.

In the only chronic oral study, gavage exposure to 108 mg/kg/day for 78 weeks caused fatty degeneration in the liver of rats (NCI 1978). Interpretation of the results is confounded by high incidences of endemic chronic murine pneumonia, but this is unlikely to have contributed to effects observed in the liver.

Renal Effects. Autopsy reports showed no evidence of damage to the kidney of humans who ingested suicidal doses of 1,1,2,2-tetrachloroethane (Mant 1953). The lack of effect can be ascribed to the rapid lethality. No other studies were located regarding renal effects in humans following oral exposure to 1,1,2,2-tetrachloroethane.

No treatment-related renal effects were seen in rats or mice administered 1,1,2,2-tetrachloroethane in the diet for 14 weeks at concentrations resulting in doses as high as 320 and 1,400 mg/kg/day, respectively (NTP 2004a). In studies conducted by the NCI (1978), rats treated with up to 108 mg/kg/day for 78 weeks showed no gross or histopathological changes in the kidney. Mice treated for the same duration at 142 mg/kg/day also showed no changes, but at 284 mg/kg/day, toxic tubular nephrosis was determined to be the probable cause of death in male mice. However, this renal effect may have been secondary to hepatocellular carcinoma noted in most of these high-dose (284 mg/kg/day) male mice.

Endocrine Effects. No studies were located regarding endocrine effects in humans after oral exposure to 1,1,2,2-tetrachloroethane. No treatment-related histopathological effects were seen in major endocrine tissues, including pituitary, thyroid, parathyroid, and adrenals of rats or mice administered 1,1,2,2-tetrachloroethane in the diet for 14 weeks at concentrations resulting in doses as high as 320 and 1,400 mg/kg/day, respectively (NTP 2004a) or in other rats or mice chronically administered the chemical (5 days/week for 78 weeks) via oral gavage at doses as high as 108 and 284 mg/kg/day, respectively (NCI 1978).

Dermal Effects. No studies were located regarding dermal effects in humans after oral exposure to 1,1,2,2-tetrachloroethane. No changes were noted in the gross appearance of skin or subcutaneous tissues in rats or mice exposed to 1,1,2,2-tetrachloroethane at doses up to 284 mg/kg/day for 78 weeks (NCI 1978).

Ocular Effects. No studies were located regarding ocular effects in humans after oral exposure to 1,1,2,2-tetrachloroethane. Squinted or reddened eyes with a reddish-brown discharge were noted in male and female rats at all dose levels treated with 1,1,2,2-tetrachloroethane for 78 weeks (NCI 1978).

Body Weight Effects. No studies were located regarding body weight effects in humans after oral exposure to 1,1,2,2-tetrachloroethane.

No treatment-related effects on body weight were seen in rats administered 1,1,2,2-tetrachloroethane in daily gavage doses up to 104 mg/kg for 21 days (NTP 1996). In a study that employed higher dose levels, oral gavage administration of 1,1,2,2-tetrachloroethane for 3–14 days in the range of 270–300 mg/kg/day resulted in body weights that were 17–55% lower than controls; no adverse body weight effects were seen at the lower doses ranging from 135 to 150 mg/kg/day (Hanley et al. 1988; NTP 1993a, 1993b). No adverse body weight effects were seen in mice administered 1,1,2,2-tetrachloroethane via oral gavage at doses as high as 300 mg/kg/day for 4 days (Hanley et al. 1988) or other mice receiving up to 1,350 mg/kg/day for 12 of 16 days (NTP 1993d). Daily doses of 178 mg/kg/day, 5 days/week for 6 weeks resulted in 38–41% depressed body weight gains in male and female rats, relative to controls; at 100 mg/kg/day, respective body weight gains were 9 and 24% less than controls (NCI 1978). In contrast, no effects on body weight gain were seen in mice similarly exposed at doses as high as 316 mg/kg/day.

Similar effect levels were reported following dietary exposure. A dietary concentration resulting in a daily dose of 300 mg/kg for 15 days resulted in a 25–29% depressed final body weights in rats (NTP 2004a). In a 14-week dietary study in rats, concentrations of 1,1,2,2-tetrachloroethane resulting in a dose level of 170 mg/kg/day caused a 29% depression in final body weight; at a dose level of 320 mg/kg/day, actual body weight loss was noted (NTP 2004a). In mice, dosing at 599 mg/kg/day for 15 days resulted in a 10–14% depressed final body weight (NTP 2004a). A 12% depression in final body weight was noted in mice receiving 370 mg/kg/day for 14 weeks; the 200 mg/kg/day level did not elicit treatment-related body weight effects (NTP 2004a). Approximately 14–18% depressed body weight was noted in male and female rats administered 1,1,2,2-tetrachloroethane via oral gavage at doses of 108 and 76 mg/kg/day, respectively; no body weight effects were seen at the lower dose (62 and 43 mg/kg/day in males and females, respectively) (NCI 1978). No treatment-related adverse body weight effects were elicited by similar treatment of male and female mice for 78 weeks at doses of 142 or 284 mg/kg/day (NCI 1978).

3.2.2.3 Immunological and Lymphoreticular Effects

One investigator reported that the results of an autopsy showed an enlarged and congested spleen in a case of intentional or accidental ingestion of 1,1,2,2-tetrachloroethane (Hepple 1927), while another autopsy study reported that the gross appearance of the spleen was normal (Elliott 1933).

Limited information is available regarding the potential for 1,1,2,2-tetrachloroethane-induced immunological or lymphoreticular effects following oral exposure. In a 14-week dietary study of rats, pigmentation of the spleen was increased in males receiving 1,1,2,2-tetrachloroethane at doses of ≥80 mg/kg/day and in females receiving doses of ≥170 mg/kg/day; high incidences (70–100%) of atrophy in the spleen (red pulp and lymphoid follicle) of both sexes were noted at 320 mg/kg/day (NTP 2004a). Relative thymus weights were reduced in rats that were exposed to 400 mg/kg/day for 15 days or 320 mg/kg/day for 14 weeks, and in mice exposed to 599 mg/kg/day for 15 days (NTP 2004a). No gross or histological alterations were seen in the spleen or lymph nodes of rats and mice exposed to 1,1,2,2-tetrachloroethane for 78 weeks at doses up to 108 and 284 mg/kg/day, respectively (NCI 1978).

3.2.2.4 Neurological Effects

Information on the neurotoxicity of oral exposure to 1,1,2,2-tetrachloroethane in humans is available from several case reports. People who intentionally ingested lethal amounts usually lost consciousness within approximately 1 hour and died 3–20 hours postingestion (Elliott 1933; Forbes 1943; Hepple 1927; Lilliman 1949; Mant 1953; Sherman 1953). Patients who were accidentally given an estimated oral dose of 68–118 mg/kg as medicinal treatment for hookworm experienced loss of consciousness and other clinical signs of narcosis that included shallow breathing, faint pulse, and pronounced lowering of blood pressure (Sherman 1953; Ward 1955). In animals, lethargy and central nervous system depression occurred in rats gavaged with 270–300 mg/kg/day for 1–12 days (Hanley et al. 1988; NTP 1993a, 1993b) or 208 mg/kg/day for 21 days (NTP 1996). Information on neurological effects of lower acute oral doses is limited to a rat study in which a single gavage dose of 100 mg/kg caused ataxia and 50 mg/kg caused decreased passive avoidance to an electric shock, possibly due to an increased threshold of shock perception due to a subtle anesthetic effect (Wolff 1978). Evaluation of this study is complicated by incomplete reporting and insufficient quantitative data, but the possible anesthetic effect suggests that 50 mg/kg is a LOAEL for neurotoxicity in rats. The LOAEL values for each reliable study for neurological effects after acute-duration exposure are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans following oral exposure to 1,1,2,2-tetrachloroethane. No gross or histological alterations in the reproductive organs of male or female rats or mice administered 1,1,2,2-tetrachloroethane by oral gavage 5 days/week for 78 weeks at doses as high as 108 and 76 mg/kg/day in male and female rats, respectively, and 284 mg/kg/day in mice (NCI 1978). Atrophy of prostate gland, seminal vesicle, and testicular germinal epithelium was noted in male rats administered 1,1,2,2-tetrachloroethane in the diet for 14 weeks at a concentration resulting in a dose level of 320 mg/kg/day; similar treatment of female rats at a dose level of 170 mg/kg/day resulted in uterine atrophy and changes in lengths of estrus cycle stages (NTP 2004a).

The highest NOAEL and all LOAEL values from all reliable studies for reproductive effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans following oral exposure to 1,1,2,2-tetrachloroethane. In a developmental toxicity report submitted to NTP (1991a), no changes in numbers of live fetuses per litter, dead fetuses per litter, resorptions per litter, or implants per litter were seen following dietary exposure of pregnant rats to 1,1,2,2-tetrachloroethane during gestation days 6–16 at maternal doses ranging from 34 to 330 mg/kg/day. One dam in the 98 mg/kg/day group and four of nine dams in the 330 mg/kg/day group completely resorbed their litters. At scheduled sacrifice, average fetal weights were statistically significantly decreased in all dose groups except the 34 mg/kg/day group (4.9, 4, 12.8, 10.6, and 20.7% decrease in the 34, 98, 180, 278, and 330 mg/kg/day groups, respectively). However, in this study, 1,1,2,2-tetrachloroethane treatment resulted in dose-related significantly decreased maternal body weight (9.3, 11.6, 13.8, and 24% lower than controls in the 98, 180, 278, and 330 mg/kg/day groups, respectively) and dose-related decreased food consumption ranging in magnitude from 16 to 60% less than that of controls. Because complete resorptions occurred only at doses resulting in significantly reduced food consumption and serious maternal body weight effects, the results of this developmental toxicity study (NTP 1991a) are not included in Table 3-2 or Figure 3-2. In a similar study report of dietary exposure of pregnant mice (NTP 1991b), the lowest exposure level (0.5% in the food; dose of approximately 987 mg/kg/day) resulted in 14% decreased maternal body weight gain during the treatment period, but no indications of developmental effects with respect to number of implantation sites, number of resorptions, numbers of dead and live fetuses, or gravid uterine weight. Exposure at higher levels resulted in maternal death, precluding assessment of treatment-related developmental toxicity at the higher doses.

3.2.2.7 Cancer

No studies were located regarding carcinogenic effects in humans following oral exposure to 1,1,2,2-tetrachloroethane.

A study in humans evaluated the possible carcinogenic effects of 1,1,2,2-tetrachloroethane in clothing-treatment workers (Norman et al. 1981). Inhalation exposure concentrations and durations were not reported, and coexposures to other chemicals and dermal exposures were likely. No increases in standard mortality ratios were found for total mortality, cardiovascular disease, cirrhosis of the liver, or cancer of the digestive and respiratory systems. The mortality ratio for lymphatic cancers was increased, although the number of deaths was small (4 cases observed compared to 0.85 expected).

Carcinogenicity of 1,1,2,2-tetrachloroethane in animals was evaluated in chronic oral studies in rats and mice (NCI 1978). The purity of the 1,1,2,2-tetrachloroethane was approximately 90% (contaminants not identified). Male and female rats were exposed to time-weighted average (TWA) doses of 0, 62, or 108 mg/kg/day (males) or 0, 43, or 76 mg/kg/day (females) by gavage 5 days/week for 78 weeks, followed by a 32-week period during which the rats were not exposed. There was a high prevalence of endemic chronic murine pneumonia in both sexes that likely contributed to early mortality that occurred in 20% of the females. No significant increases in tumor incidences were observed in the rats. Male and female B6C3F1 mice were similarly exposed to TWA doses of 0, 142, or 284 mg/kg/day for 78 weeks, followed by a 12-week period during which the mice were not exposed. Survival was markedly decreased after 45 weeks of exposure in the high-dose male and female mice; the cause of death appeared to be acute toxic tubular nephrosis in the males but was not reported in the females. Significant, dose-related increases in the incidence of hepatocellular carcinoma were observed in the male mice (3/36, 13/50, and 44/49 in the control, low-dose, and high-dose groups, respectively) and female mice (1/40, 30/48, and 43/47, respectively).

The EPA has classified the carcinogenicity of 1,1,2,2-tetrachloroethane as Group C, possible human carcinogen (IRIS 2006). The EPA (IRIS 2006) calculated an oral slope factor of 0.2 $(mg/kg/day)^{-1}$ for 1,1,2,2-tetrachloroethane (verified June 26, 1986), based on the NCI (1978) study showing increased hepatocellular carcinomas in female mice. This q_1* corresponds to upper bound individual lifetime cancer risks ranging from $5x10^{-4}$ mg/kg/day (10^{-4} risk level) to $5x10^{-7}$ mg/kg/day (10^{-7} risk level). These risk levels are indicated on Figure 3-2.

3.2.3 Dermal Exposure

3.2.3.1 Death

One human death was reported when a man cleaned up a 1,1,2,2-tetrachloroethane spill with his bare hands (Coyer 1944). He was also exposed to unmeasured levels of 1,1,2,2-tetrachloroethane vapors.

The dermal LD_{50} (lethal dose, 50% kill) for 1,1,2,2-tetrachloroethane in rabbits is 6,360 mg/kg (Smyth et al. 1969).

3.2.3.2 Systemic Effects

Since humans dermally exposed to 1,1,2,2-tetrachloroethane invariably were reported to have considerable inhalation exposure as well, separation of effects due solely to dermal exposure could not be determined. Those exposed to 1,1,2,2-tetrachloroethane in the workplace showed cardiovascular, gastric, hematological, and hepatic disturbances as noted in the discussion on systemic effects due to inhalation exposure discussed in Section 2.2.1.2 (Coyer 1944; Lobo-Mendonca 1963; Minot and Smith 1921). Total exposure levels and effects due to inhalation versus dermal exposure were not determined in these studies, but air concentrations were reported to vary from 9 to 98 ppm in one study (Lobo-Mendonca 1963).

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, and renal effects in animals after dermal exposure to 1,1,2,2-tetrachloroethane.

Dermal Effects. Direct application of 514 mg/cm^2 of 1,1,2,2-tetrachloroethane for 16 hours damaged the skin of guinea pigs, causing karyopyknosis and pseudoeosinophilic infiltration (Kronevi et al. 1981). Application of 1,1,2,2-tetrachloroethane (concentration not reported) to the shaved abdomen of rabbits caused hyperemia, edema, and severe blistering (Dow 1944). Smyth et al. (1969) similarly found that application of 1,1,2,2-tetrachloroethane to the uncovered abdomen of rabbits caused local skin irritation (severity of 6 on a scale of 1–10).

Ocular Effects. Humans exposed to 1,1,2,2-tetrachloroethane vapors (130 ppm) for 10 minutes experienced mucosal irritation around the eyes (Lehmann and Schmidt-Kehl 1936). Similarly, guinea pigs exposed to 576 ppm for 5 minutes demonstrated eye closure and squinting; by 15 minutes, lacrimation was common (NIOSH 1978). Rats showed these effects at 5,050 ppm. These ocular effects are due to direct contact of the eyes with the vapors rather than a true systemic effect due to inhalation of the vapor. No studies were located in which liquid 1,1,2,2-tetrachloroethane was instilled directly into the eye.

3.2.3.3 Immunological and Lymphoreticular Effects

Data on the immunological and lymphoreticular effects in humans and animals following dermal exposure are limited. One person who died following dermal exposure to 1,1,2,2-tetrachloroethane had an enlarged spleen with nodular areas on its surface (Coyer 1944). This individual cleaned up a spill with his bare hands, and the nature and extent of the exposure were poorly defined.

No dermal hypersensitivity tests in guinea pigs or other kinds of studies were located regarding immunological or lymphoreticular effects in animals after dermal exposure to 1,1,2,2-tetrachloroethane.

3.2.3.4 Neurological Effects

Workers in India's bangle industry who dipped their hands into 1,1,2,2-tetrachloroethane and inhaled it had tremors and vertigo in addition to gastric disturbances (Lobo-Mendonca 1963). Specific exposure levels were not measured, but air concentrations were measured at between 9 and 98 ppm. The incidence of tremors was higher among factory workers exposed to higher concentrations, suggesting a dose-response relationship. Workers in an artificial silk plant experienced fatigue, irritability, headache, and coma (Minot and Smith 1921). Exposure levels were not estimated.

No studies were located regarding neurological effects in animals following dermal application of 1,1,2,2-tetrachloroethane.

No studies were located regarding the following effects in humans or animals following dermal exposure to 1,1,2,2-tetrachloroethane:

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

3.3 GENOTOXICITY

No studies were located regarding genotoxic effects in humans following inhalation, oral, or dermal exposure to 1,1,2,2-tetrachloroethane. *In vitro* and *in vivo* tests of genotoxicity of 1,1,2,2-tetrachloroethane have produced mixed results, as discussed below and summarized in Tables 3-3 and 3-4.

1,1,2,2-Tetrachloroethane has been shown to be predominantly inactive in reverse mutation assays in *Salmonella typhimurium* (strains TA97, TA98, TA100, TA1530, TA1535, TA1537, and TA1538), either with or without the addition of S9 metabolic activating mixture, even at concentrations that lead to

Table 3-3. Genotoxicity of 1,1,2,2-Tetrachloroethane *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	References
Salmonella typhimurium	Reverse mutation	–	–	Haworth et al. 1983
		–[a]	–[a]	Milman et al. 1988
		–[a,b]	–[a,b]	Nestmann et al. 1980
		–[c]	–[c]	NTP 2004a
		–	–	Ono et al. 1996
		–[a]	–[a]	Mitoma et al. 1984
		–[a]	–[a]	Warner et al. 1988
		Not tested	+[a,c]	Brem et al. 1974
		Not tested	+[a,c]	Rosenkranz 1977
		+[d]	+[d]	Strobel and Grummt 1987
	Forward mutation	–[b]	–[b]	Roldan-Arjona et al. 1991
Saccharomyces cerevisiae	Gene mutation	Not tested	+[b]	Callen et al. 1980
		Not tested	–	Nestmann and Lee 1983
Escherichia coli	DNA growth, repair, or synthesis	Not tested	+[a,d]	Brem et al. 1974
		Not tested	+[a,d]	Rosenkranz 1977
		+[d]	–[d]	DeMarini and Brooks, 1992
Aspergillus nidulans	Mitotic cross-over	Not tested	–[b]	Crebelli et al. 1988
	Aneuploidy	Not tested	+[b]	Crebelli et al. 1988
L5178Y mouse lymphoma cells	Gene mutation	–[b]	–[b]	NTP 2004a
Chinese hamster ovary cells	Chromosomal aberrations	–[b]	–[b]	Galloway et al. 1987
		–[b]	–[b]	NTP 2004a
Chinese hamster ovary cells	Sister chromatid exchange	+[b]	+[b]	Galloway et al. 1987
		+[b]	+[b]	NTP 2004a
BALB/c 3T3 mouse cells	Sister chromatid exchange	+[b]	+[b]	Colacci et al. 1992
	Cell transformation	Not tested	–[a,b]	Arthur D. Little Inc. 1983
		Not tested	–[a,b]	Tu et al. 1985
		–[a]	–[a]	Milman et al. 1988
		+[b]	+[b]	Colacci et al. 1990
	Promotion of cell transformation	Not tested	–[b]	Colacci et al. 1996
Rat hepatocytes	DNA growth, repair, or synthesis	Not tested	–[a,b]	Milman et al. 1988
		Not tested	–[a,b]	Naylor Dana Institute 1983
Mouse hepatocytes	DNA growth, repair, or synthesis	Not tested	–[a,b]	Milman et al. 1988
		Not tested	–[a,b]	Naylor Dana Institute 1983
Human embryonic intestinal cells	DNA growth, repair, or synthesis	–	Not tested	NIOSH 1980

[a]Adjusted for volatility
[b]Tested up to cytotoxic concentrations
[c]Not adjusted for volatility
[d]Cytotoxic concentrations not included

– = negative result; + = positive result

Table 3-4. Genotoxicity of 1,1,2,2-Tetrachloroethane *In Vivo*

Species/test system	End point	Result	Reference
Drosophila melanogaster	Sex-linked recessive lethal mutation	–	NIOSH 1980; NTP 2004a; Woodruff et al. 1985
	Mitotic recombination	–	Vogel and Nivard 1993
Mouse hepatocytes	Unscheduled DNA synthesis	+	Miyagawa et al. 1995
Mouse hepatocytes, male	Unscheduled DNA synthesis	–	Mirsalis et al. 1989
	S-Phase DNA synthesis	–	Mirsalis et al. 1989
Mouse hepatocytes, female	Unscheduled DNA synthesis	–	Mirsalis et al. 1989
	S-Phase DNA synthesis	+/–	Mirsalis et al. 1989
Rat bone marrow cells, male	Chromosomal aberrations	–	NIOSH 1980
Rat bone marrow cells, female	Chromosomal aberrations	+	NIOSH 1980
Mouse peripheral blood erythrocytes	Micronucleus formation	+	NTP 2004a

+ = active; – = inactive; +/– = equivocal

cytotoxicity (Haworth et al. 1983; Milman et al. 1988; Mitoma et al. 1984; Nestmann et al. 1980; NTP 2004a; Ono et al. 1996; Warner et al. 1988). However, a few studies reported reverse mutation activity in *S. typhimurium* (Brem et al. 1974; Rosenkranz 1977; Strobel and Grummt 1987). Results of studies employing methods to prevent volatilization were not notably different from those that did not use those methods. 1,1,2,2-Tetrachloroethane also did not induce forward mutations (L-arabinose resistance) in *S. typhimurium* strain BA13 (Roldan-Arjona et al. 1991). Assays with *Escherichia coli* indicated that 1,1,2,2-tetrachloroethane induced DNA damage, as shown by growth inhibition in DNA polymerase deficient *E. coli* (Brem et al. 1974; Rosenkranz 1977) and induction of prophage lambda (DeMarini and Brooks 1992). In *Saccharomyces cerevisiae*, 1,1,2,2-tetrachloroethane induced gene conversion, reversion, and recombination in one study (Callen et al. 1980), whereas another study found no conversion or reversion (Nestmann and Lee 1983). In *Aspergillus nidulans*, 1,1,2,2-tetrachloroethane induced aneuploidy, but no crossing over (Crebelli et al. 1988).

1,1,2,2-Tetrachloroethane did not induce trifluorothymidine resistance in L5178Y mouse lymphoma cells, with or without S9, at concentrations up to those producing lethality (NTP 2004a). Primary hepatocytes from rats and mice exposed *in vitro* to 1,1,2,2-tetrachloroethane did not show altered DNA repair at concentrations that were not cytotoxic (Milman et al. 1988; Naylor Dana Institute 1983). NIOSH (1980) reported no increase in unscheduled DNA synthesis (UDS) in human embryonic intestinal fibroblasts exposed to 1,1,2,2-tetrachloroethane. Treatment of Chinese hamster ovary (CHO) cells with up to 653 µg/mL (which was cytotoxic) did not result in increased induction of chromosomal aberrations, but did produce an increased frequency of sister chromatid exchanges (SCEs) at concentrations of 55.8 µg/mL or higher (Galloway et al. 1987; NTP 2004a). SCEs were also induced in BALB/c-3T3 cells treated *in vitro* with high concentrations (500 µg/mL or higher) of 1,1,2,2-tetrachloroethane, either with or without S9 activating mixture (Colacci et al. 1992).

In BALB/c-3T3 cells, 1,1,2,2-tetrachloroethane exposure of up to 250 µg/mL in the absence of exogenous metabolic activation did not result in increased numbers of transformed cells (Arthur D. Little Inc. 1983; Colacci et al. 1992; Milman et al. 1988; Tu et al. 1985); survival was generally 70% or higher. Higher doses (500 µg/mL or more) were capable of transforming the cells, but also showed higher levels of cytotoxicity (Colacci et al. 1990). In the presence of exogenous metabolic activation, however, even relatively low levels (31.25 µg/mL) of 1,1,2,2-tetrachloroethane used as an initiating agent, followed by promotion with 12-O-tetradecanoylphorbol-13-acetate (TPA), resulted in increased numbers of transformed cells (Colacci et al. 1992). 1,1,2,2-Tetrachloroethane did not act as a promoter in BALB/c-3T3 cells *in vitro* without metabolic activation (Colacci et al. 1996).

1,1,2,2-Tetrachloroethane tested negative for sex-linked recessive lethal mutations and mitotic recombination in *Drosophila melanogaster* (NIOSH 1980; NTP 2004a; Vogel and Nivard 1993; Woodruff et al. 1985). Replicative DNA synthesis was increased in hepatocytes isolated from male B6C3F1 mice exposed to a single gavage dose of 200 mg/kg (24 and 48 hours postexposure) or 400 mg/kg (24, 39, and 48 hours postexposure) relative to hepatocytes from unexposed mice (Miyagawa et al. 1995). Hepatocytes isolated from mice following a single gavage dose of up to 1,000 mg/kg did not show an increase in UDS or S-phase DNA synthesis (Mirsalis et al. 1989). Inhalation exposure to 5 or 50 ppm (34.3 or 343 mg/m^3) for 7 hours/day, 5 days/week did not result in increased frequency of chromosomal aberrations in bone marrow cells isolated from male rats (NIOSH 1980); female rats exposed to 50 ppm (343 mg/m^3), but not to 5 ppm (34.3 mg/m^3), showed an increase in bone marrow cell aberrations other than gaps (NIOSH 1980). Covalent binding of radiolabeled 1,1,2,2-tetrachloroethane to DNA, ribonucleic acid (RNA), and protein in the liver, kidney, lung, and stomach occurred in rats and mice exposed to a single intravenous dose and analyzed 22 hours postexposure (Colacci et al. 1987).

3.4 TOXICOKINETICS

In both humans and laboratory animals, 1,1,2,2-tetrachloroethane is well absorbed from the respiratory and gastrointestinal tracts, and is absorbed through the skin of animals after dermal exposure. When administered by oral or inhalation routes, 1,1,2,2-tetrachloroethane is extensively metabolized and excreted chiefly as metabolites in the urine and breath. In rats and mice, 1,1,2,2-tetrachloroethane is metabolized to trichloroethanol, trichloroacetic acid, and dichloroacetic acid, which is then broken down to glyoxylic acid, oxalic acid, and carbon dioxide; a small percentage of the dose is expired in the breath as the parent compound and as carbon dioxide. In reductive and oxidative metabolism, 1,1,2,2-tetrachloroethane is known to produce reactive radical and acid chloride intermediates, respectively.

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

While studies of the systemic toxicity of 1,1,2,2-tetrachloroethane following inhalation in humans are indicative of some level of systemic absorption, comparatively few studies have quantitatively addressed this issue. A study in volunteers was carried out in which a bulb containing [38Cl]-labeled 1,1,2,2-tetrachloroethane was inserted into their mouths; they immediately inhaled deeply, held their breaths for

20 seconds, and then exhaled through a trap containing granulated charcoal. The study showed that 97% of a single breath of 1,1,2,2-tetrachloroethane was absorbed systemically (Morgan et al. 1970). The accuracy of this value is unclear because the procedure used to measure uptake is unorthodox and high retention of volatile organic compounds on the charcoal was not validated. Additionally, there were other potential sources of 1,1,2,2-tetrachloroethane loss and inexact measurements (e.g., volume of air exhaled across the trap) that could affect the results. Two subjects were reported to retain approximately 40–60% of inspired 1,1,2,2-tetrachloroethane after a 30-minute exposure of up to 2,300 mg/m^3 (Lehmann and Schmidt-Kehl 1936), but additional details were not provided.

The total body burden of radioactivity in male Osborne-Mendel rats and B6C3F1 mice exposed to 10 ppm (68.7 mg/m^3) of ^{14}C-1,1,2,2-tetrachloroethane vapor for 6 hours (Hanley et al. 1988) was 38.7 µmol equivalents per kg in rats (9.50 µmol equivalents and using a body weight of 245 g from the study) and 127 µmol equivalents per kg in mice (3.059 µmol equivalents and using a body weight of 24.1 g from the study), indicating that the mice absorbed proportionally more 1,1,2,2-tetrachloroethane on a per-body-weight basis. Between 92 and 98% of the body burdens were recovered as metabolites, indicating that very high uptake of the 10 ppm exposure occurred in both species. Ikeda and Ohtsuji (1972) detected metabolites in the urine of rats exposed to 200 ppm (1,370 mg/m^3) of 1,1,2,2-tetrachloroethane, indicating that absorption had occurred, but did not provide a quantitative estimate of absorption rate or fraction. Similarly, Gargas and Andersen (1989) followed the elimination of 1,1,2,2-tetrachloroethane from the blood after a 6-hour exposure to 350 ppm (2,400 mg/m^3), but did not provide quantitative estimates of absorption.

3.4.1.2 Oral Exposure

Studies that quantify absorption following oral exposure in humans were not available. The profound effect of ingestion of large amounts of 1,1,2,2-tetrachloroethane indicates that appreciable amounts are absorbed.

Observations in animals also indicate that the oral absorption of 1,1,2,2-tetrachloroethane is rapid and extensive. Cottalasso et al. (1998) reported hepatic effects only 15–30 minutes following a single oral exposure in rats. Following a single oral exposure of male Osborne-Mendel rats and B6C3F1 mice to 150 mg/kg of radiolabeled 1,1,2,2-tetrachloroethane in corn oil, only 4–6% of the activity was recovered in the feces 72 hours postexposure, while >90% of the administered activity was found in both species as metabolites, indicating that the compound was nearly completely absorbed in both rats and mice within

72 hours (Hanley et al. 1988). Mitoma et al. (1985) exposed groups of male Osborne-Mendel rats to 25 or 100 mg/kg and B6C3F1 mice to 50 or 200 mg/kg of 1,1,2,2-tetrachloroethane, 5 days/week for 4 weeks followed by a single radiolabeled dose of the compound, and evaluated its disposition over the next 48 hours. While absorption was not quantified, 79% of the dose was metabolized in rats and 68% was metabolized in mice, suggesting that at least those levels of compound had been absorbed within 48 hours. In an abstract, Milman et al. (1984) noted that rats and mice that received 1,1,2,2-tetrachloroethane orally absorbed most of the dose; no further details were available on this study.

3.4.1.3 Dermal Exposure

No studies were located regarding absorption following dermal exposure in humans.

Up to 1 mL of 1,1,2,2-tetrachloroethane applied to the skin of mice or guinea pigs was absorbed within a half hour (dose site sealed to prevent evaporation) (Jakobson et al. 1982; Tsuruta 1975).

3.4.2 Distribution

No studies were located regarding distribution in humans following inhalation, oral, or dermal exposure to 1,1,2,2-tetrachloroethane.

Following absorption in animals, 1,1,2,2-tetrachloroethane appears to be distributed throughout the body, but may selectively accumulate to a degree in certain cells and tissues. The human blood-air partition coefficient for 1,1,2,2-tetrachloroethane has been reported to be in the range of 72.6–116 (Gargas et al. 1989; Meulenberg and Vijverberg 2000; Morgan et al. 1970). The large blood-air partition coefficient contributes to low exhaled breath concentrations of unmetabolized 1,1,2,2-tetrachloroethane (Section 3.4.4). Although 1,1,2,2-tetrachloroethane is well metabolized (Section 3.4.3), the fraction that is metabolized would be less if the blood-air partition coefficient was less. The tissue:air partition coefficients for 1,1,2,2-tetrachloroethane in rats have been reported to be 142 (blood), 3,767 (fat), 196 (liver), and 101 (muscle) (Gargas et al. 1989), indicating that 1,1,2,2-tetrachloroethane is likely to partition into fatty tissues, consistent with its low water solubility.

A high level of hepatic protein-binding radioactivity was seen in mice administered 1,1,2,2-tetrachloroethane by gavage, followed by a single dose of ^{14}C-1,1,2,2-tetrachloroethane. The amount of

1,1,2,2-tetrachloroethane-derived radioactivity covalently bound to liver protein was about 2 times that seen in rats (Mitoma et al. 1985). The difference in toxicity of 1,1,2,2-tetrachloroethane in rats and mice may well be due to the higher metabolic rate in mice.

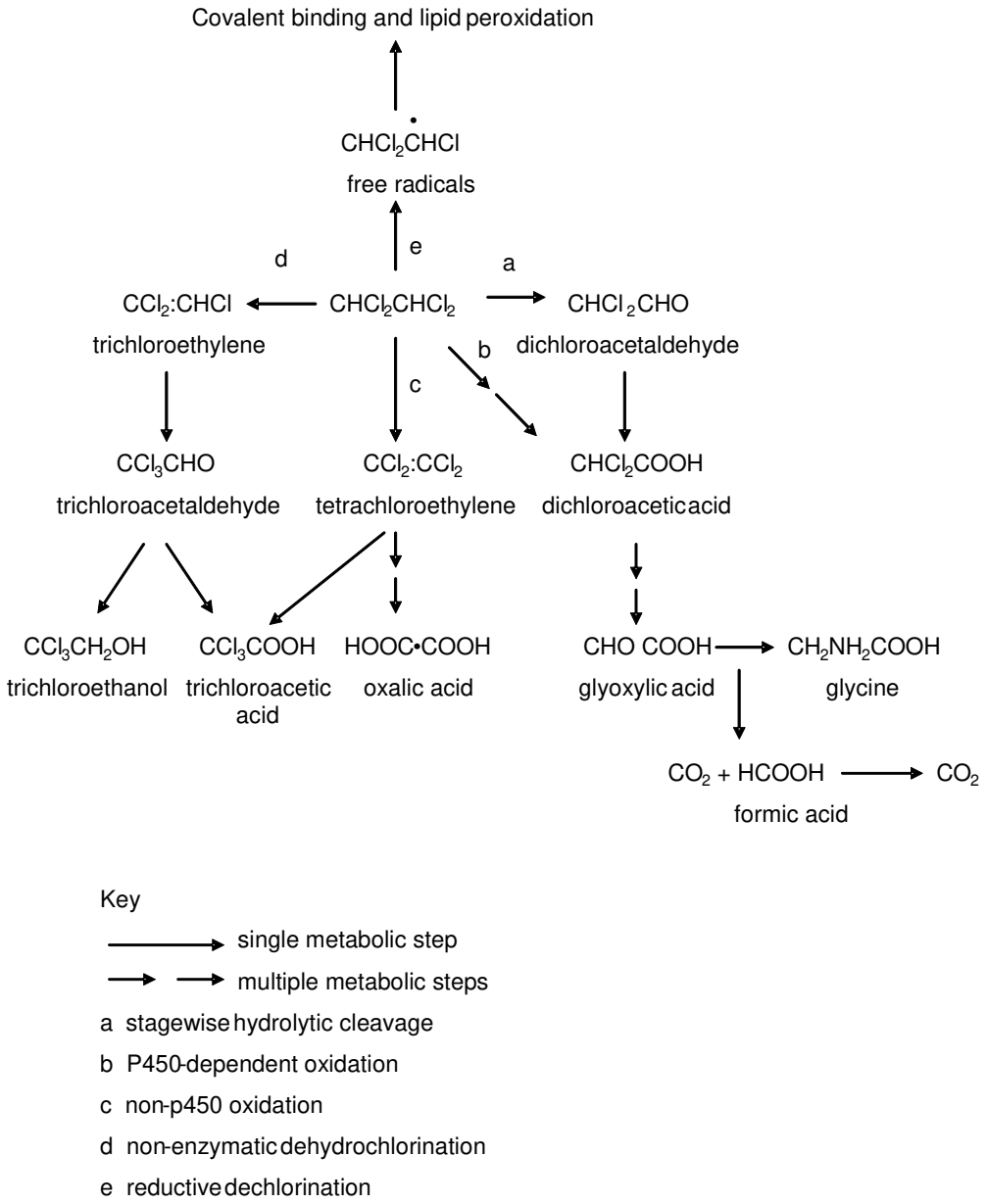
Following a single intravenous injection of radiolabeled 1,1,2,2-tetrachloroethane, Eriksson and Brittebo (1991) reported that a high and selective uptake of nonvolatile radioactivity occurred in the mucosal tissues of olfactory and tracheobronchial regions of the respiratory tract and in the mucosae of the oral cavity, tongue, nasopharynx, esophagus, and cardiac region of the forestomach. High levels of activity were also found in the liver, bile, inner zone of the adrenal cortex, and interstitium of the testis, although the levels were not quantified.

3.4.3 Metabolism

No studies were located regarding metabolism of 1,1,2,2-tetrachloroethane in humans following inhalation, oral, or dermal exposure.

Information regarding 1,1,2,2-tetrachloroethane metabolism in animals is summarized below, and a metabolic scheme based on *in vivo* and *in vitro* data in rodents is presented in Figure 3-3. *In vivo* and *in vitro* studies indicate that the metabolism of 1,1,2,2-tetrachloroethane proceeds via multiple pathways in rodents (Casciola and Ivanetich 1984; Halpert 1982; Halpert and Neal 1981; Ikeda and Ohtsuji 1972; Koizumi et al. 1982; Mitoma et al. 1985; Yllner 1971). The predominant pathway appears to involve production of dichloroacetic acid, formed as an initial metabolite via stagewise hydrolytic cleavage of 1,1,2,2-tetrachloroethane (nonenzymatic degradation yielding dichloroacetyl chloride and dichloro-acetaldehyde as intermediates), or by cytochrome P450-based oxidation of 1,1,2,2-tetrachloroethane (Halpert and Neal 1981; Yllner 1971). Dichloroacetic acid was identified as the major urinary metabolite in mice treated with 1,1,2,2-tetrachloroethane by intraperitoneal injection (Yllner 1971) and in *in vitro* systems with rat liver microsomal and nuclear cytochrome P450 (Casciola and Ivanetich 1984; Halpert 1982; Halpert and Neal 1981). Dichloroacetic acid can be further metabolized to glyoxylic acid, formic acid, and carbon dioxide (Yllner 1971), with carbon dioxide a potential major component of the end products (Mitoma et al. 1985; Yllner 1971). Other pathways involve the formation of trichloroethylene or tetrachloroethylene as initial metabolites, with subsequent reactions yielding trichloroethanol, trichloroacetic acid, and oxalic acid as important end products (Ikeda and Ohtsuji 1972; Mitoma et al. 1985; Yllner 1971).

Figure 3-3. Suggested Metabolic Pathways of 1,1,2,2-Tetrachloroethane



Metabolism of 1,1,2,2-tetrachloroethane is generally extensive, with 68% or more of a total administered dose found as metabolites (Hanley et al. 1988; Mitoma et al. 1985; Yllner 1971). Mice that were given a single 0.16–0.32 g/kg intraperitoneal dose of ^{14}C-labeled 1,1,2,2-tetrachloroethane eliminated 45–61% of the administered radioactivity as carbon dioxide in the expired air and 23–34% of the radioactivity in urine in the following 3 days (Yllner 1971). Dichloroacetic acid, trichloroacetic acid, trichloroethanol, oxalic acid, glyoxylic acid, and urea accounted for 27, 4, 10, 7, 0.9, and 2% (mean) of the urinary radioactivity excreted in 24 hours, respectively. In rats, trichloroethanol appeared to be present as a urinary metabolite at approximately 4-fold greater levels than trichloroacetic acid following a single 8-hour inhalation exposure (Ikeda and Ohtsuji 1972). Several studies have reported that metabolism of 1,1,2,2-tetrachloroethane is greater in mice than in rats; the magnitudes of the reported differences are generally in the range of a 1.1–3.5-fold greater metabolic activity, on a per-kg basis, in mice (Hanley et al. 1988; Milman et al. 1984; Mitoma et al. 1985).

As indicated above, cytochrome P450-based metabolism of 1,1,2,2-tetrachloroethane to dichloroacetic acid has been demonstrated *in vitro*. Multiple P450 isozymes are likely to be involved, as demonstrated by studies reporting increased metabolism and covalent binding of metabolites following pretreatment with phenobarbital (Casciola and Ivanetich 1984; Halpert 1982), xylene (Halpert 1982), or ethanol (Sato et al. 1980); isozymes induced by these chemicals include members of the CYPIIA, CYPIIB, CYPIIE, and CYPIIIA subfamilies (Nebert et al. 1987; Omiecinski et al. 1999). Pretreatment with acetone did not appear to alter the toxicity of 1,1,2,2-tetrachloroethane, although cytochrome P450 levels were not evaluated (Charbonneau et al. 1991). 1,1,2,2-Tetrachloroethane also has been reported to cause inactivation of cytochrome P450. 1,1,2,2-Tetrachloroethane effectively inactivated the major phenobarbital-inducible P450 isozyme, but not the major P450 isozyme induced by β-naphthoflavone, in rat liver *in vitro* (Halpert et al. 1986). Rat liver nuclear cytochrome P450 activity was reduced following *in vitro* incubation with 1,1,2,2-tetrachloroethane and a NADPH-generating system (Casciola and Ivanetich 1984). In an *in vivo* study, cytochrome P450 activity was evaluated in male and female Swiss Albino mice 24 hours after a single 0, 300, or 600 mg/kg intraperitoneal dose of 1,1,2,2-tetrachloroethane (Paolini et al. 1992). 1,1,2,2-Tetrachloroethane treatment reduced total cytochrome P450 activity significantly in both sexes at both dose levels, suggesting that it may act as a suicide inhibitor of the enzyme. Treatment with 600 mg/kg reduced the microsomal activity of P450 isozymes IIIA, IIE1, IA2, IIB1, and IA1 in both sexes, and 300 mg/kg reduced the activity of P450IIIA in both sexes and P450IIB1 in males. The only evidence of a significant role for glutathione was the observation of a 17% reduction

in glutathione S-transferase (GST) activity toward 1-chloro-2,4-dinitrobenzene (a general GST substrate) in mice of the 600 mg/kg dose group.

Following an intravenous injection of radiolabeled 1,1,2,2-tetrachloroethane, parts of the radioactivity could not be extracted from liver, adrenal cortex, and testis, indicating the presence of covalently bound metabolites (Eriksson and Brittebo 1991) and implicating the formation of free radical intermediates during the metabolic process; the formation of free radicals from 1,1,2,2-tetrachloroethane metabolism has been demonstrated in spin-trapping experiments (Paolini et al. 1992; Tomasi et al. 1984). The observation of covalent binding to tissues is supported by the studies of Hanley et al. (1988), which reported significant levels of covalent binding in hepatic tissues after inhalation of radiolabeled 1,1,2,2-tetrachloroethane; mice were found to have approximately a 1.9-fold greater extent of hepatic covalent binding than rats, which the study authors noted was consistent with the greater metabolism, on a per-kg basis, in mice compared to rats. Other findings suggested that at least a portion of the binding of radiolabel in liver DNA in mice exposed to a single 150 mg/kg oral dose of ^{14}C-1,1,2,2-tetrachloroethane may have been from metabolic breakdown (Hanley et al. 1988). After a 4-week oral exposure of unlabeled 1,1,2,2-tetrachloroethane followed by a single oral dose of labeled 1,1,2,2-tetrachloroethane, Mitoma et al. (1985) also reported greater levels of tissue covalent binding in mice compared to rats; the differences were on the order of 2-fold greater binding in mice, which would be consistent both with the Hanley et al. (1988) studies and with the observed differences in metabolism of the two species discussed above. This may also be related to the 3.2–3.5-fold greater absorption, on a per-kg basis, following inhalation exposure to mice than to rats (Hanley et al. 1988).

The kinetic constants of 1,1,2,2-tetrachloroethane metabolism in rats exposed to 350 ppm of the chemical for 6 hours were determined in gas uptake studies performed by Gargas and Andersen (1989). The rate of exhalation of 1,1,2,2-tetrachloroethane was measured and, combined with previously published values for partition coefficients for blood/air, liver/blood, muscle/blood, and fat/blood, allowed the successful estimation of the disposition of the chemical in rat (Gargas et al. 1989). A K_m of 4.77 μM and a V_{max} of 12 mg/hour (scaled to a l-kg rat) were measured.

3.4.4 Elimination and Excretion

Available animal data indicate that following absorption into the body, 1,1,2,2-tetrachloroethane is eliminated mainly as metabolites in urine and carbon dioxide and unchanged compound in expired air (Gargas and Andersen 1989; Hanley et al. 1988; Ikeda and Ohtsuji 1972; Mitoma et al. 1985; Yllner

1971). The patterns of elimination in rats and mice are qualitatively similar (Hanley et al. 1988; Mitoma et al. 1985), although covalent binding is somewhat greater in mice than rats. Elimination is fairly rapid, with significant amounts present in the urine and expired air at 48–72 hours postexposure (Hanley et al. 1988; Ikeda and Ohtsuji 1972; Mitoma et al. 1985; Yllner 1971).

Covalent binding of metabolites of 1,1,2,2-tetrachloroethane may result in delays in elimination, as reflected in high levels of compound detected in the carcass of animals. Milman et al. (1984) reported in an abstract that 45% of the activity from a single radiolabeled oral dose of 1,1,2,2-tetrachloroethane was recovered in the carcass, although the evaluation time was not reported. A later study by the same authors (Mitoma et al. 1985) reported a 30.75% retention in the carcass of rats and a 27.44% retention in the carcass of mice 48 hours after exposure to a single labeled dose of 1,1,2,2-tetrachloroethane. Hanley et al. (1988) reported 30% retention in the carcass in rats exposed to 10 ppm by inhalation, 25% in mice exposed to 10 ppm by inhalation, 23% in rats exposed to 150 mg/kg by gavage, and 17.3% in mice exposed to 150 mg/kg by gavage. Colacci et al. (1987) reported covalent binding of radiolabeled 1,1,2,2-tetrachloroethane to DNA, RNA, and protein in the liver, kidney, lung, and stomach of rats and mice exposed to a single intravenous dose and analyzed 22 hours postexposure. *In vitro* binding to calf thymus DNA was found to be greatest when the microsomal fraction was present, and was inhibited by SKF-525A, indicating that metabolic activation was likely required for DNA binding (Colacci et al. 1987).

3.4.4.1 Inhalation Exposure

A study on volunteers showed that 3% of inhaled 1,1,2,2-tetrachloroethane was excreted in the breath, and that the urinary excretion rate was 0.015% of the absorbed dose/minute (Morgan et al. 1970).

The excretion of 1,1,2,2-tetrachloroethane was tracked for 72 hours following exposure of rats and mice to vapor concentrations of 10 ppm ^{14}C-1,1,2,2-tetrachloroethane for 6 hours (Hanley et al. 1988). More than 90% of the absorbed dose was metabolized in both species. The percentage of the recovered radioactivity was reported as follows: in rats, 33% in breath (25% as CO_2 and 8% as unchanged compound), 19% in urine, and 5% in feces; in mice, 34% in breath (32% as CO_2 and 2% as unchanged compound), 26% in urine, and 6% in feces. Radioactivity in urine and feces was nonvolatile (inferred by the researchers to be product(s) of metabolism), but was not otherwise characterized.

3.4.4.2 Oral Exposure

No studies were located regarding excretion in humans following oral exposure to 1,1,2,2-tetrachloroethane.

The excretion of 1,1,2,2-tetrachloroethane was followed for 72 hours following oral administration of 150 mg/kg doses to rats and mice (Hanley et al. 1988). Greater than 90% of the absorbed dose was metabolized in both species. In rats, 41% was excreted in breath (32% as CO_2 and 9% as unchanged compound), 23% in urine, and 4% in feces. In mice, 51% was excreted in breath, 22% in urine, and 6% in feces. Radioactivity in urine and feces was nonvolatile (inferred by the researchers to be product(s) of metabolism), but was not otherwise characterized.

Mice given an oral dose of 1,1,2,2-tetrachloroethane excreted about 10% of the dose unchanged in the breath. The rest was metabolized and excreted in the breath as CO_2 (10%), in the urine and feces (30%, measured together), and retained in the carcass (27%) after 48 hours. Rats showed similar patterns of excretion (Mitoma et al. 1985).

3.4.4.3 Dermal Exposure

No studies were located regarding excretion in humans following dermal exposure to 1,1,2,2-tetrachloroethane.

A study describing the elimination of 1,1,2,2-tetrachloroethane in guinea pigs demonstrated that, following dermal absorption, about half of the 1,1,2,2-tetrachloroethane in the blood is eliminated in 2 hours (Jakobson et al. 1982).

3.4.4.4 Other Routes of Exposure

The most comprehensive study of the metabolism and excretion of 1,1,2,2-tetrachloroethane was an intraperitoneal study in mice using ^{14}C-labeled 1,1,2,2-tetrachloroethane. This study showed that after 72 hours, about 4% of the radioactivity was expired unchanged in the breath, 50% was expired as CO_2, 28% was excreted in the urine, 1% was in the feces, and 16% remained in the carcass (Yllner 1971).

3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan 1994; Andersen et al. 1987). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parameterization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) are adequately described, however, this simplification is desirable because data are often unavailable for

many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-4 shows a conceptualized representation of a PBPK model.

If PBPK models for 1,1,2,2-tetrachloroethane exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

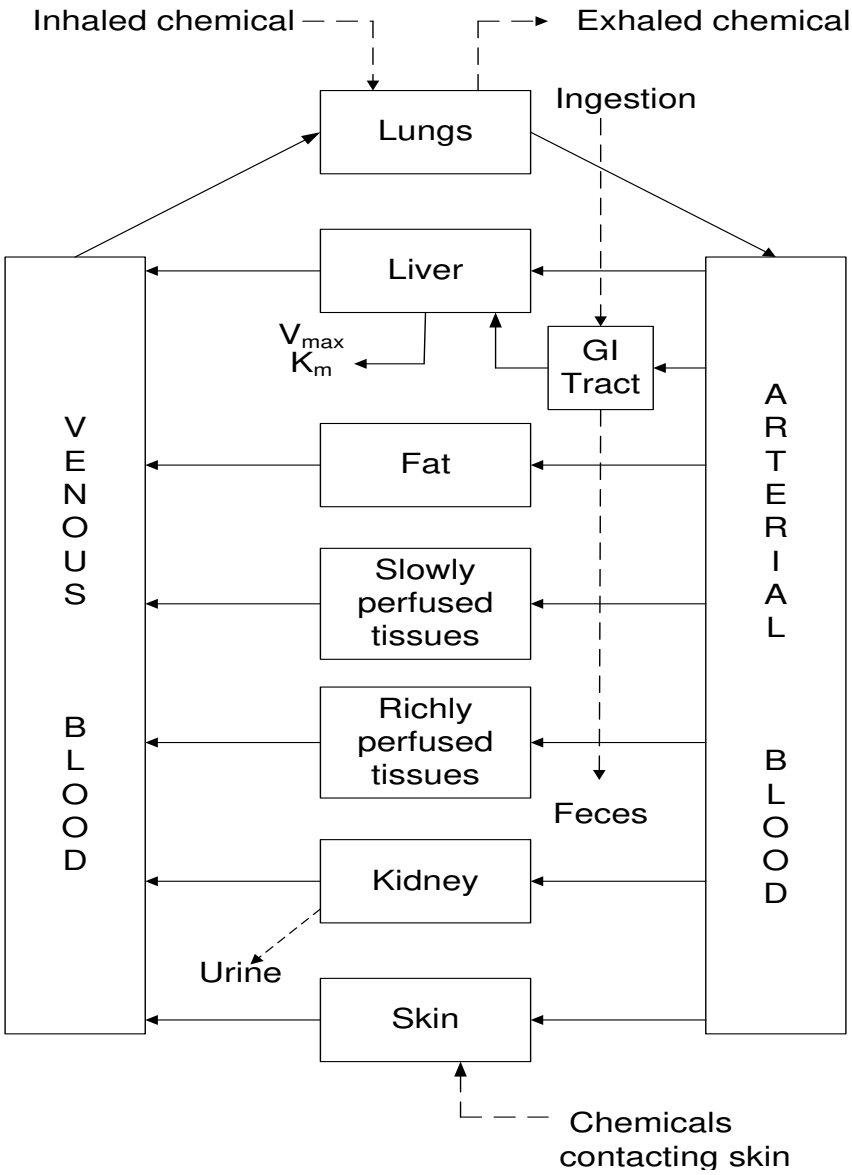
Gargas and Andersen (1989) described using a modified PBPK model for styrene (Ramsey and Anderson 1984) and measurements of parent compound in exhaled breath of previously-exposed rats to estimate *in vivo* kinetic constants for 1,1,2,2-tetrachloroethane. However, no PBPK models specific to 1,1,2,2-tetrachloroethane were located.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

Based upon its physical and chemical properties (a low molecular weight and highly lipophilic volatile organic compound), 1,1,2,2-tetrachloroethane is likely to be rapidly and extensively absorbed following both oral and inhalation exposures. This expectation is consistent with reported absorption of 70–100% in oral animal studies (Hanley et al. 1988; Mitoma et al. 1985) and 40–97% in human inhalation studies (Lehmann and Schmidt-Kehl 1936; Morgan et al. 1970), although the human data are uncertain due to unorthodox and dated study protocols that were used to assess uptake. Because 1,1,2,2-tetrachloroethane is a volatile, lipophilic molecule of small molecular size that appears to be readily absorbed from the respiratory and gastrointestinal tracts, passive diffusion is the most likely mechanism of absorption.

Figure 3-4. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

Source: adapted from Krishnan and Andersen 1994

Following absorption, 1,1,2,2-tetrachloroethane is readily distributed throughout the body, although the high tissue:air partition coefficient for fat (Gargas et al. 1989) suggests that 1,1,2,2-tetrachloroethane may accumulate more in lipid-rich tissues. Distribution likely occurs predominantly via passive diffusion. Metabolism of 1,1,2,2-tetrachloroethane is extensive, with 68% or more of a total administered dose generally found as metabolites (Hanley et al. 1988; Mitoma et al. 1985; Yllner 1971). The metabolism of 1,1,2,2-tetrachloroethane, as well as covalent binding of reactive metabolites to protein and DNA, is likely to be most prominent in the liver.

Urinary elimination occurs mainly as metabolites, including glyoxalic acid, formic acid, trichloroethanol, and trichloroacetic acid, while a fraction of an absorbed dose may be eliminated in the expired air as parent compound or carbon dioxide (Gargas and Andersen 1989; Hanley et al. 1988; Ikeda and Ohtsuji 1972; Mitoma et al. 1985; Yllner 1971). Passive diffusion is the most likely major mechanism of excretion. Covalent binding of metabolites of 1,1,2,2-tetrachloroethane (Colacci et al. 1987; Hanley et al. 1988; Milman et al. 1984; Mitoma et al. 1985) may result in delays in elimination.

3.5.2 Mechanisms of Toxicity

Metabolism of 1,1,2,2-tetrachloroethane to reactive products is likely to play a key role in its toxicity. Both nuclear and microsomal cytochrome P450 enzymes have been implicated in the metabolism of the compound, possibly releasing a number of biologically active compounds, including aldehydes, alkenes, acids, and free radicals (see Figure 3-3 in Section 3.3) that may react with biological tissues. Evidence for metabolism to reactive compounds comes from studies of binding of radiolabeled 1,1,2,2-tetrachloroethane to tissues that was enhanced by pretreatment with phenobarbital, xylene, or ethanol; the variety of inducers capable of influencing this effect suggests that multiple P450 isozymes may be involved. Additionally, mice are known to metabolize 1,1,2,2-tetrachloroethane at a 1.1–3.5-fold greater rate than rats (Hanley et al. 1988; Milman et al. 1984; Mitoma et al. 1985) and have been demonstrated to have approximately 2-fold greater covalent binding to tissues (Mitoma et al. 1985), further implicating metabolic activation as a possible mode of action. Thus, for tissues high in metabolic capacity, such as the liver, the formation of active metabolites is a likely mechanism for the toxicity of 1,1,2,2-tetrachloroethane.

The presence of the functional group consisting of a terminal dichloromethyl moiety in a molecule, as typified by the drug chloramphenicol, is known to confer toxicity. Chloramphenicol and other dichloromethyl compounds are hydroxylated to form, after spontaneous dehydrohalogenation, reactive

acyl chloride intermediates (Halpert 1981; Halpert et al. 1986), which subsequently bind to crucial proteins to exert their effects. Alternately, these acid chlorides can hydrolyze to form their respective acids. There was clear evidence in the literature reviewed that these pathways were operant for 1,1,2,2-tetrachloroethane. Cytochrome P-450 was found to catalyze the formation of both dichloroacetylated protein adducts (Halpert 1982) and dichloroacetic acid (Halpert 1981). These biotransformation reactions were increased by chronic ethanol consumption and fasting, preconditions that are known to induce the levels of cytochrome P-450 isoenzyme IIE1 (Johansson et al. 1988; Soucek and Gut 1992). Significantly, a number of low molecular weight volatile halocarbons are metabolized by this isoform, suggesting that it may be the major contributor to the metabolism of 1,1,2,2-tetrachloroethane as well (Guengerich et al. 1991).

As part of an investigation into the reductive metabolism of 1,1,2,2-tetrachloroethane in mice, Paolini and coworkers trapped a carbon-centered radical formed *in vivo* by reductive dehalogenation of 1,1,2,2-tetrachloroethane, a reaction presumably mediated by cytochrome P-450 (Paolini et al. 1992). Tomasi et al. (1984) demonstrated the formation of free radicals from 1,1,2,2-tetrachloroethane metabolism as well. Paolini et al. (1992) also identified conjugated diene hydroperoxides formed in endoplasmic reticulum of mice that had been exposed to 600 mg/kg 1,1,2,2-tetrachloroethane. Collectively, these findings are indicative of a mechanism of action whereby 1,1,2,2-tetrachloroethane metabolism could result in the reductive formation of radical products, leading to the stimulation of lipid peroxidation and its attendant hepatotoxic effects, a scenario that has been demonstrated for the structurally-related chlorinated alkane,carbon tetrachloride. Additionally, both dichloro- and trichloroacetic acids are known to cause proliferation of peroxisomes (DeAngelo et al. 1986). In the work presented by Hanley et al. (1988), this property of the acid metabolites of 1,1,2,2-tetrachloroethane was noted, and suggested as a possible mechanism by which the halocarbon could elicit hepatotoxic responses.

The mechanism behind the neurological effects of high-dose exposures to 1,1,2,2-tetrachloroethane has not been well characterized. While it is possible that metabolic activation may play a role in causing these effects, studies of similar compounds suggest that the parent compound may be the causative agent. In general, the highly lipophilic nature of chlorinated hydrocarbons, such as 1,1,2,2-tetrachloroethane, allows them to cross the blood-brain barrier readily and partition into lipids in neuronal membranes. This property allows them to interfere with neural membrane function, bringing about central nervous system depression, behavioral changes, and anesthesia (Klaassen 1996). Recent studies indicate that most compounds used as general anesthetics are capable of modulating neurotransmitter-gated ion channels, particularly receptors for GABA and glutamate, at clinical concentrations (Hemmings et al. 2005). It is

feasible that 1,1,2,2-tetrachloroethane could act in a similar manner, although studies describing the mechanism of 1,1,2,2-tetrachloroethane-induced neurological effects are not available.

The mode of action of the carcinogenic effects of 1,1,2,2-tetrachloroethane is incompletely characterized. Genotoxicity studies provide only limited evidence of a genotoxic mode of action. 1,1,2,2-Tetrachloroethane has weak genotoxic activity, with *in vitro* genotoxicity tests generally reporting negative results except for assays of SCE and cell transformation; *in vivo* tests of genotoxicity have shown a similar pattern. 1,1,2,2-Tetrachloroethane has been shown to bind to DNA in the liver and several other organs organs in rats and mice *in vivo* (Colacci et al. 1987; Hanley et al. 1988), indicating that this mechanism may contribute to the carcinogenic process. Several studies of 1,1,2,2-tetrachloroethane toxicity have reported increases in the number of hepatocytes in mitosis, but the possible role these effects may have on the carcinogenicity of 1,1,2,2-tetrachloroethane has not been evaluated. The results of rat liver preneoplastic foci and mouse BALB/c-3T3 cell neoplastic transformation assays suggest that 1,1,2,2-tetrachloroethane may have initiating and promoting activity (Colacci et al. 1992, 1996; Milman et al. 1988; Story et al. 1986), but tumor initiation and promotion studies have not been conducted to elucidate these potential modes of action.

It is likely that tumor formation by 1,1,2,2-tetrachloroethane involves metabolism to one or more active compounds, that in turn result in carcinogenicity. 1,1,2,2-Tetrachloroethane is metabolized extensively following absorption, presumably at least in part by cytochrome P450 enzymes. Urinary metabolites of 1,1,2,2-tetrachloroethane include dichloroacetic acid, trichloroacetic acid, trichloroethylene, and tetrachloroethylene (Section 3.4.3). Chronic exposure of rats and mice to trichloroacetic acid, trichloroethylene, and tetrachloroethlyene had similar effects as were reported in the NCI (1978) carcinogenicity study of 1,1,2,2-tetrachloroethane, with hepatic tumors in male and female mice but not in rats of either sex (Bull et al. 1990; Herren-Freund et al. 1987; NCI 1976, 1977; NTP 1986, 1990; Pereira 1996; Pereira and Phelps 1996). Dichloroacetic acid has also been demonstrated to cause hepatocellular tumors in both male and female mice (Bull et al. 1990; Daniel et al. 1992; DeAngelo et al. 1991, 1999; Pereira 1996; Pereira and Phelps 1996); dichloroacetic acid has been shown to cause liver tumors in rats as well, but the results are not as striking as in mice (DeAngelo et al. 1996; Richmond et al. 1995). Dichloroacetic acid, trichloroacetic acid, trichloroethylene, and tetrachloroethylene have similar genotoxicity profiles as 1,1,2,2-tetrachloroethane, adding further support to the possibility that metabolism to one or more of these compounds may be involved in the carcinogenicity of 1,1,2,2-tetrachloroethane. Mice are known to metabolize 1,1,2,2-tetrachloroethane to a greater extent than rats, which may in part account for the fact that liver tumors occurred in mice, but not in rats, following chronic oral

exposure. Although it is plausible that the carcinogenicity of 1,1,2,2-tetrachloroethane involves metabolism to one or more active compounds, there is no direct evidence linking one or more metabolites to its carcinogenic effects.

In addition to being metabolized to carcinogenic compounds, 1,1,2,2-tetrachloroethane may be metabolized to form free radicals, which can, in turn, covalently bind to tissues, including DNA. Formation of free radicals during 1,1,2,2-tetrachloroethane metabolism has been demonstrated in spin-trapping experiments (Paolini et al. 1992; Tomasi et al. 1984). Both nuclear and microsomal forms of cytochrome P450 enzymes have been implicated in this process, as increased metabolism and covalent binding of metabolites following pretreatment with phenobarbital (Casciola and Ivanetich 1984; Halpert 1982), xylene (Halpert 1982), or ethanol (Sato et al. 1980) have been reported. The presence of covalently bound label has been reported following inhalation (Hanley et al. 1988), oral (Mitoma et al. 1985), and intravenous (Eriksson and Brittebo 1991) administration of radiolabeled 1,1,2,2-tetrachloroethane.

3.5.3 Animal-to-Human Extrapolations

Limited information is available regarding the pharmacokinetic properties of 1,1,2,2-tetrachloroethane in humans. Species-specific differences in pharmacokinetic properties of 1,1,2,2-tetrachloroethane have been demonstrated in rats and mice. Results of Hanley et al. (1988) indicate a 3.2–3.5-fold greater absorption of 1,1,2,2-tetrachloroethane (on a per-kg basis) in mice than rats following inhalation exposure. Several studies have reported that metabolism of 1,1,2,2-tetrachloroethane is greater in mice than in rats; the magnitudes of the reported differences are generally in the range of a 1.1–3.5-fold greater metabolic activity in mice (Hanley et al. 1988; Milman et al. 1984; Mitoma et al. 1985). After a 4-week oral exposure of unlabeled 1,1,2,2-tetrachloroethane followed by a single oral dose of labeled 1,1,2,2-tetrachloroethane, Mitoma et al. (1985) also reported greater levels of tissue covalent binding in mice compared to rats; the differences were on the order of 2-fold greater binding in mice.

Based on pharmacokinetic differences between rats and mice and limited human pharmacokinetic data for 1,1,2,2-tetrachloroethane, animal-to-human extrapolations include considerable uncertainty. Because metabolism of 1,1,2,2-tetrachloroethane is greater in mice than rats, it is reasonable to expect that mice might be more susceptible than rats to 1,1,2,2-tetrachloroethane toxicity. In general, the order of metabolic rates for other chlorinated solvents is mice>rats>humans.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to *as endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Thomas and Colborn (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents.* The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

No human data were located regarding the potential for 1,1,2,2-tetrachloroethane to affect the endocrine system. Based on available animal data, the endocrine system does not appear to be a target of 1,1,2,2-tetrachloroethane toxicity (Gohlke and Schmidt 1972; Horiuchi et al. 1962; NCI 1978; NIOSH 1978; NTP 2004a). However, it should be noted that test data for classical and emerging neuroendocrine endpoints (e.g., hormone levels, receptor binding/mediated assays, etc.) are not presently available for

1,1,2,2-tetrachloroethane. Furthermore, available animal data are limited due to relatively crude assessment of reproductive and endocrinological endpoints (i.e., histopathology of reproductive and endocrine tissues and effects on sperm parameters).

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6, Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life, and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water, and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and

Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

Studies in humans and animals have not examined the effect of 1,1,2,2-tetrachloroethane exposure on the immature organism. The limited data evaluating the effect of 1,1,2,2-tetrachloroethane on developing rats and mice have not indicated effects on the offspring at levels that did not also cause maternal effects (NTP 1991a, 1991b; Schmidt et al. 1972). Because metabolism of 1,1,2,2-tetrachloroethane to reactive products is likely to play a key role in 1,1,2,2-tetrachloroethane toxicity, potential age-related differences in metabolism could result in age-related differences in susceptibility to the toxic effects of exposure to 1,1,2,2-tetrachloroethane. For example, the well-recognized metabolic immaturity of hepatic enzymes during infancy (Ginsberg et al. 2002, 2004) might be protective against 1,1,2,2-tetrachloroethane-induced liver effects since these effects appear to require hepatic metabolism. How this would ultimately affect risk is difficult to predict since the ability to remove toxic metabolites may also be immature.

The mechanism behind the neurological effects of high-dose exposures to 1,1,2,2-tetrachloroethane is not well characterized, but studies of similar compounds suggest that the parent compound may be the causal agent (Section 3.5.2). The amount of parent 1,1,2,2-tetrachloroethane that has the opportunity to reach the central nervous system and produce neurotoxicity may be greater in infants than adults. Reasons for this include immaturity in hepatic metabolism (which could lead to longer-half life of parent compound, higher blood levels and thus greater amounts reaching the central nervous system), and immaturity of the blood-brain barrier (which could result in increased distribution into the central nervous system).

Children may be more vulnerable to 1,1,2,2-tetrachloroethane since intake dose per kilogram of body weight may be greater in early life than in mature humans, because children eat more food, drink more water, breathe more air, and ingest more soil/house dust per kilogram body weight than older age groups (EPA 2002; NRC 1993). There are no reports on levels of 1,1,2,2-tetrachloroethane in breast milk (Section 6.6). PBPK models for similar chlorinated solvents (e.g., Fisher et al. 1997) suggest that 1,1,2,2-tetrachloroethane may not present a particularly large breast milk concern for nursing infants, largely because of its rapid metabolism by the maternal system.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to 1,1,2,2-tetrachloroethane are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial

cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by 1,1,2,2-tetrachloroethane are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10, Populations That Are Unusually Susceptible.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to 1,1,2,2-Tetrachloroethane

There currently are no specific biomarkers available to quantify exposure to 1,1,2,2-tetrachloroethane. Metabolites of 1,1,2,2-tetrachloroethane, including trichloroacetic acid, trichloroethanol, and trichloroethanol glucuronide, may be measured in blood and urine (Breimer et al. 1974; Christensen et al. 1988; Koppen et al. 1988) (see Chapter 7). However, these metabolites are produced by other common chlorinated alkanes and would not be specifically indicative of exposure to 1,1,2,2-tetrachloroethane. Also, available animal data indicate that 1,1,2,2-tetrachloroethane is rapidly metabolized and excreted, primarily within the first 3 days postexposure (Yllner 1971). Therefore, tests for the presence of 1,1,2,2-tetrachloroethane or its metabolites would only be useful if performed shortly following exposure.

3.8.2 Biomarkers Used to Characterize Effects Caused by 1,1,2,2-Tetrachloroethane

There currently are no biomarkers available to characterize effects caused by 1,1,2,2-tetrachloroethane. However, since 1,1,2,2-tetrachloroethane has the potential to cause liver damage at high doses, it may be possible to correlate changes in urinary metabolites with serum indicators of liver malfunction, although the metabolites would not be specific for 1,1,2,2-tetrachloroethane. 1,1,2,2-Tetrachloroethane has been shown to bind to DNA in the liver (and to a lesser extent the kidney, lung, and stomach) of rats and mice *in vivo* (Colacci et al. 1987; Hanley et al. 1988), suggesting that it may be plausible to use DNA adducts in peripheral blood lymphocytes as a biomarker of effects (as has been done for numerous genotoxic agents).

3.9 INTERACTIONS WITH OTHER CHEMICALS

In efforts to find treatments for acute-duration 1,1,2,2-tetrachloroethane poisoning, various substances have been tested to determine if they altered the toxicity of 1,1,2,2-tetrachloroethane in rats (Laass 1973a, 1973b, 1974a, 1974b). The survival times were increased when 1,1,2,2-tetrachloroethane was administered with castor oil, but decreased when administered orally with milk. Survival time was also decreased when 1,1,2,2-tetrachloroethane was given with mineral oil or with paraffin.

Alcohol, an inducer of cytochrome P-450 form IIE1, increased the metabolism of 1,1,2,2-tetrachloroethane (Sato et al. 1980) and intensified the effects of 1,1,2,2-tetrachloroethane in rats (Gohlke and Schmidt 1972). This indicates that humans who consume alcohol may be at increased risk for toxic effects from 1,1,2,2-tetrachloroethane. This is also the case for several other chlorinated aliphatic hydrocarbons. However, although alcohol combined with 1,1,2,2-tetrachloroethane increased the relative weight of the testes in rats (Schmidt et al. 1972), it did not alter the effects of 1,1,2,2-tetrachloroethane on the histopathology or function in the liver, nor was there damage to the kidneys, spleen, adrenals, brain, or thyroid.

The potentiation of haloalkane-induced liver injury by acetone is a well-known phenomenon, as readily demonstrated in acetone-pretreated rats exposed to trichloroethylene-carbon tetrachloride mixture. Charbonneau et al. (1991) assessed the influence of acetone pretreatment on the severity of liver injury in rats administered various other haloalkane mixtures intraperitoneally. Acetone pretreatment did not increase the severity of liver injury induced by binary mixtures that included 1,1,2,2-tetrachloroethane. Whereas apparent additive hepatotoxicity was elicited by some of the tested binary mixtures that did not include 1,1,2,2-tetrachloroethane, binary mixtures of 1,1,2,2-tetrachloroethane and either 1,1-dichloroethylene or tetrachloroethylene appeared to be less hepatotoxic than 1,1-dichloroethylene or tetrachloroethylene alone, possibly due to competitive inhibition of metabolism.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to 1,1,2,2-tetrachloroethane than will most persons exposed to the same level of 1,1,2,2-tetrachloroethane in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of 1,1,2,2-tetrachloroethane, or compromised function of organs affected by 1,1,2,2-tetrachloroethane. Populations who

are at greater risk due to their unusually high exposure to 1,1,2,2-tetrachloroethane are discussed in Section 6.7, Populations with Potentially High Exposures.

As metabolism is believed to play an important role in the toxicity of 1,1,2,2-tetrachloroethane, particularly in the liver, individuals with elevated levels of cytochrome P450 enzymes may have an increased susceptibility to the compound. Halpert (1982) reported an increase in *in vitro* metabolite formation and in covalently bound metabolites following pretreatment with xylene or phenobarbital, both of which increased cytochrome P450 activity. Sato et al. (1980) similarly reported an increased metabolism of 1,1,2,2-tetrachloroethane in rats following ethanol pretreatment. Since 1,1,2,2-tetrachloroethane has been demonstrated to inhibit cytochrome P450 enzymes (Halpert 1982; Paolini et al. 1992), presumably through a suicide inhibition mechanism, it is also possible that people coexposed to chemicals that are inactivated by cytochrome P450 enzymes will be more susceptible to those compounds. Because the liver and nervous system are the main targets of 1,1,2,2-tetrachloroethane toxicity, individuals with compromised function of liver or nervous system may be at increased risk from exposure to 1,1,2,2-tetrachloroethane.

Studies directly evaluating sex-related differences in toxicity following exposure to 1,1,2,2-tetrachloroethane are not available. Toxicity studies that evaluated both sexes in the same study did not show consistent sex-related differences.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to 1,1,2,2-tetrachloroethane. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to 1,1,2,2-tetrachloroethane. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to 1,1,2,2-tetrachloroethane:

Ellenhorn MJ, Schonwald S, Ordog G, et al. 1997. 1,1,2,2-Tetrachloroethane. Ellenhorn's medical toxicology: Diagnosis and treatment of human poisoning. 2nd ed. Baltimore, MD: Williams and Wilkins, 1436-1440.

Goldfrank LR, Flomenbaum NE, Lewin NA, et al. 2002. Hydrocarbons. In: Goldfrank's toxicologic emergencies. New York, NY: McGraw Hill, 1303-1322.

Haddad LM, Shannon MW, Winchester JF. 1998. Clinical management of poisoning and drug overdose. 3rd edition. Philadelphia, PA: W.B Saunders Company, 931-939.

Parraga M, West JM. 1998. Hydrocarbons. In: Viccellio P, ed. Emergency toxicology. 2nd edition. Philadelphia, PA: Lippincott-Raven Publishers, 299-313.

3.11.1 Reducing Peak Absorption Following Exposure

Human exposure to 1,1,2,2-tetrachloroethane may occur by inhalation, ingestion, or dermal contact. Concentrated vapors are irritating to the eyes and upper respiratory tract, and once absorbed can cause central nervous system and respiratory depression. Unprotected skin exposure can cause defatting and subsequent dermatitis. Suggested treatment for exposed individuals includes moving them to fresh air and administering 100% humidified supplemental oxygen. The potential risk of rapid central nervous system and respiratory depression usually outweighs the potential risk (e.g., aspiration of vomitus) of administering syrup of ipecac to induce emesis (TOMES 1993). Once in the care of a health professional, gastric lavage is suggested if it can be performed within minutes of the exposure to reduce the amount of absorbed solvent.

Following acute high-level exposure to some chlorinated solvents by any route, hypotension and cardiac arrhythmias due to myocardial sensitization to catecholamines have led to ventricular fibrillation and death (TOMES 1993). There is no specific treatment for 1,1,2,2-tetrachloroethane exposure except for supportive measures to combat the effects of central nervous system and respiratory depression, and cardiac arrhythmias.

3.11.2 Reducing Body Burden

The body does not retain significant amounts of 1,1,2,2-tetrachloroethane. Currently, there is no recognized treatment to enhance elimination. The orthodox treatment for ingestion is entirely supportive. One potential method for enhancing elimination is to increase the ventilation rate, thereby enhancing elimination via the lung. In a 6-year-old boy who had ingested 12–16 g of tetrachloroethylene, controlled hyperventilation over a 5-day period enhanced pulmonary excretion of the chemical (Koppel et al. 1985). This technique may be applicable to other volatile solvents like 1,1,2,2-tetrachloroethane, although its effectiveness for clearing 1,1,2,2-tetrachloroethane from the body is likely to be lower than for tetrachloroethylene, because tetrachloroethylene is particularly slowly metabolized (providing a better opportunity for clearance via exhalation) and has a much lower human blood-air partition coefficient

(10.3–19.8 [Agency for Toxic Substances and Disease Registry 1997] compared to 72.6–116 [Section 3.4.2]).

Stimulation of the metabolism of 1,1,2,2-tetrachloroethane may also lead to enhanced elimination, but it can also result in formation of larger amounts of toxic metabolites. Thus, the risks of this approach may outweigh the benefits.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

Clinical effects caused by acute 1,1,2,2-tetrachloroethane exposure include central nervous system depression, nephritis, and toxic hepatitis (HSDB 2006). Other effects include malaise, dizziness, fatigue, headache, and lightheadedness, all of which may disappear rapidly after the exposure ceases. The mechanism of action for the central nervous system effects has not been clearly established, but it is probable that it is related to solvent effects on neuronal membranes exerted by many halogenated aliphatic hydrocarbons.

Ethanol in alcoholic beverages may compete with or enhance the metabolic activation of solvents and could possibly increase the severity of health effects, particularly liver toxicity. Alcoholic beverages should be avoided by persons exposed to 1,1,2,2-tetrachloroethane and other solvents of this nature.

Mechanisms have been proposed for the hepatotoxic action of this halocarbon (Halpert 1981; Halpert et al. 1986; Hanley et al. 1988). These include generation of reactive free radicals and acid chlorides. Dietary antioxidants may modulate the toxicity caused by the former, but no established treatments are available for the latter. It is concluded that avoiding co-exposures to substances that enhance the activation of 1,1,2,2-tetrachloroethane (e.g., acetone and ethanol) provide the best means of interfering with the toxification of the absorbed chemical.

3.12 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 1,1,2,2-tetrachloroethane is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is

required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 1,1,2,2-tetrachloroethane.

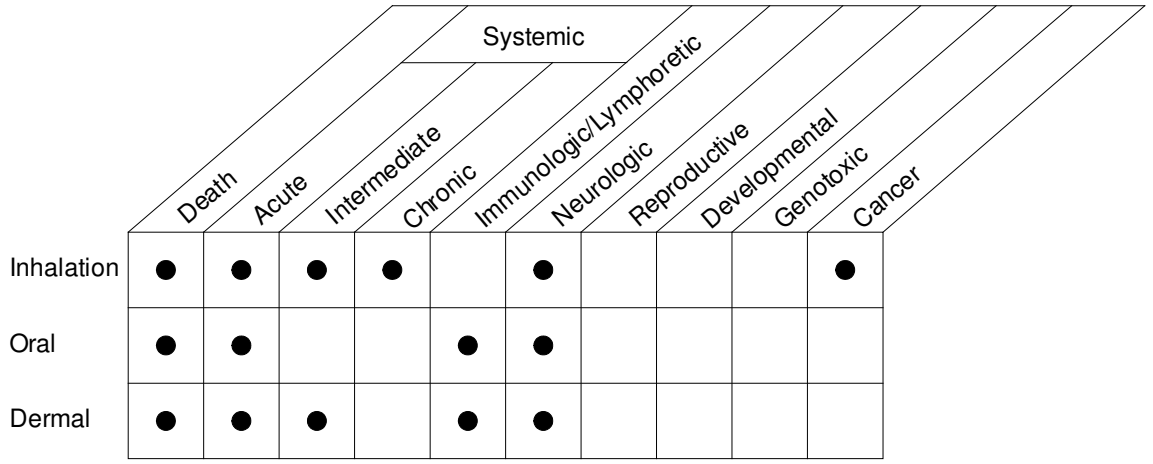
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

3.12.1 Existing Information on Health Effects of 1,1,2,2-Tetrachloroethane

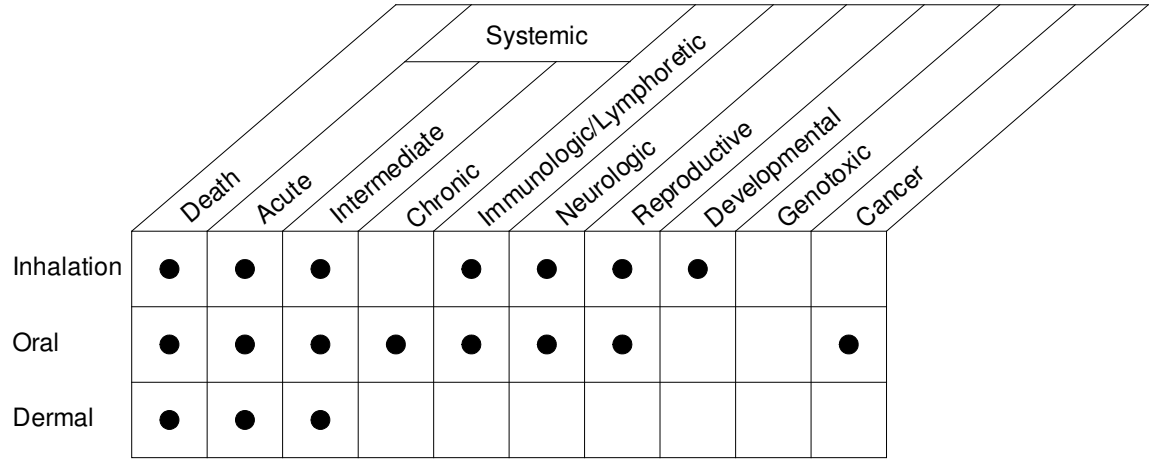
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to 1,1,2,2-tetrachloroethane are summarized in Figure 3-5. The purpose of this figure is to illustrate the existing information concerning the health effects of 1,1,2,2-tetrachloroethane. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

As seen in Figures 3-5, data exist for inhalation exposure of humans for death, systemic effects of acute-, intermediate-, and chronic-duration exposure, neurological effects, and cancer. A few human deaths have been reported following excessive inhalation exposure to 1,1,2,2-tetrachloroethane in occupational settings. Effects reported in humans exposed in the workplace consist of gastric distress including pain, nausea, vomiting, loss of appetite, and loss of body weight; increases in the number of white blood cells; jaundice, enlarged liver, liver degeneration, and cirrhosis; neurological symptoms such as headache, tremors, dizziness, numbness, and drowsiness; and possibly genital cancer and leukemia or lymphoma. In one experimental inhalation study, male volunteers experienced mucosal irritation, nausea, vomiting, and dizziness upon exposure to high levels of 1,1,2,2-tetrachloroethane. Data for oral exposure of humans consist mainly of case reports of suicidal or accidental ingestion of 1,1,2,2-tetrachloroethane, with data for death, systemic effects of acute-duration exposure, immunological/lymphoreticular, and neurological effects. Autopsy findings in suicide cases included congestion and edema in the lungs and

Figure 3-5. Existing Information on Health Effects of 1,1,2,2-Tetrachloroethane



Human



Animal

● Existing Studies

lung collapse, mucosal congestion of the esophagus and upper stomach, and epicardial and endocardial anoxic hemorrhage. In cases of humans accidentally given oral doses of 1,1,2,2-tetrachloroethane for parasite treatment, effects consisted of shallow breathing, pronounced lowering of blood pressure, and faint pulse during ensuing unconsciousness. One death was reported when a man cleaned up a 1,1,2,2-tetrachloroethane spill with his bare hands. Workers in India's bangle industry who dipped their hands in 1,1,2,2-tetrachloroethane, as well as inhaled it, had tremors, headache, and dizziness in addition to gastric disturbances. Mucosal irritation of the eyes has also been observed in humans exposed to 1,1,2,2-tetrachloroethane in air by direct contact of the concentrated vapor with the eyes.

For animals exposed by inhalation, data exist for death; systemic effects of acute- and intermediate-duration; and immunological/lymphoreticular, neurological, reproductive, and developmental effects. Systemic effects consisted of labored respiration, hematological effects, and hepatic effects. Immunological effects consisted of a decrease in titer and an increase in the electrophoretic mobility of specific antibodies to typhoid in rabbits and are considered of questionable toxicological significance. Neurological effects included decreased motor activity, loss of reflexes, ataxia, prostration, and narcosis. Limited information is available regarding reproductive or developmental endpoints in animals following inhalation of 1,1,2,2-tetrachloroethane. Data for oral exposure of animals exist for death; systemic effects of acute-, intermediate-, and chronic-duration exposure; immunological/lymphoreticular, neurological, and reproductive effects; and cancer. Systemic effects consisted of hepatic, thyroid, and adrenal effects, and decreases in body weight gain. Information on immunological/lymphoreticular effects is limited to histopathological effects on the spleen. Neurological effects consisted of central nervous system depression, debilitation, and decreased avoidance learning. An oral study in rats indicated an effect on spermatogenesis; however, the interpretation of the study was confounded by the fact that the rats had been maintained at a high temperature (35 °C). Cancer data consist of a significantly increased incidence of hepatocellular carcinoma in mice exposed orally. Existing data in animals exposed dermally to 1,1,2,2-tetrachloroethane are limited to an LD_{50} in rabbits; karyopyknosis and pseudoeosinophilic infiltration in guinea pigs; and eye closure, squinting, and lacrimation in guinea pigs and rats acutely exposed to the vapors.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. Numerous studies are available regarding the effects of acute-duration exposures to 1,1,2,2-tetrachloroethane, both in humans (Coyer 1944; Hepple 1927; Lehmann and Schmidt-Kehl 1936; Lilliman 1949; Mant 1953; Sherman 1953; Ward 1955) and animals (Cottalasso et

al. 1998; Deguchi 1972; Hanley et al. 1988; Horiuchi et al. 1962; Horvath and Frantik 1973; NTP 1991a, 1991b, 1993a, 1993b, 2004a; Pantelitsch 1933; NIOSH 1978; Schmidt et al. 1980a; Tomokuni 1969, 1970; Wolff 1978). These studies have identified the liver and central nervous system as the major organ systems affected in both humans and animals following inhalation and oral exposure.

Information on the toxicity of acute inhalation exposure to 1,1,2,2-tetrachloroethane in humans comes from a poorly reported experimental study in which two volunteers self-inhaled various concentrations of the chemical for up to 30 minutes (Lehmann and Schmidt-Kehl 1936). The results of this study suggest that 3 ppm was the odor detection threshold, 13 ppm was tolerated without effect for 10 minutes, and 146 ppm for 30 minutes or 336 ppm for 10 minutes caused irritation of the mucous membranes, pressure in the head, vertigo, and fatigue. Other early reports similarly indicate that common symptoms of high-dose acute inhalation exposure to 1,1,2,2-tetrachloroethane include drowsiness, nausea, headache, and weakness, and at extremely high concentrations, jaundice, unconsciousness, and respiratory failure (Coyer 1944; Hamilton 1917).

The preponderance of information on the acute inhalation toxicity of 1,1,2,2-tetrachloroethane in animals pertains to neurological and hepatic effects of near-lethal to lethal exposures (Carpenter et al. 1949; Horiuchi et al. 1962; Pantelitsch 1933; NIOSH 1978; Schmidt et al. 1980b). Death was typically preceded by signs of central nervous system toxicity (e.g., incoordination, loss of reflexes, labored respiration, prostration, and loss of consciousness), and postmortem examinations mainly showed congestion and fatty degeneration of the liver. Hepatotoxicity (Gohlke and Schmidt 1972; Schmidt et al. 1972, 1980a; Tomokuni 1969, 1970) and neurotoxicity (Horvath and Frantik 1973; NIOSH 1978) have been reported in animals acutely exposed to nonlethal concentrations of 1,1,2,2-tetrachloroethane vapors.

Information on the acute oral toxicity of 1,1,2,2-tetrachloroethane in humans is available from several case reports. In reports of intentional ingestion of lethal amounts of 1,1,2,2-tetrachloroethane (Elliott 1933; Forbes 1943; Hepple 1927; Lilliman 1949; Mant 1953; Sherman 1953), subjects usually lost consciousness within approximately 1 hour and died 3–20 hours postingestion, depending on the amount of food in the stomach. Postmortem examinations showed gross congestion in the esophagus, stomach, kidneys, spleen, and trachea, gross congestion and edema in the lungs, and histological effects of congestion and cloudy swelling in the lungs, liver, and/or kidneys (Hepple 1927; Mant 1953).

The preponderance of information on the acute-duration oral toxicity of 1,1,2,2-tetrachloroethane in animals is provided by gavage studies of rats and mice in which lethality was one of the end points

evaluated. LD_{50} values in rats range from 250 to 800 mg/kg (Gohlke et al. 1977; NTP 2004a; Schmidt et al. 1980a; Smyth et al. 1969). Lethality data are available for repeated gavage exposure in rats (NTP 1993a, 1996) and mice (NTP 1993d). Dietary exposure for acute and intermediate exposure durations caused moribundity or death in rats (NTP 2004a) and mice (NTP 1991b, 2004a). Information is available on acute neurological, body weight, and liver effects in animals following acute-duration oral exposure to 1,1,2,2-tetrachloroethane (Cottalasso et al. 1998; Hanley et al. 1988; NTP 1993a, 1993b, 2004a; Schmidt et al. 1980a; Wolff 1978), but most adverse changes were observed at near-lethal to lethal dose levels.

In summary, derivation of acute-duration inhalation and oral MRLs for 1,1,2,2-tetrachloroethane are precluded by the lack of information regarding threshold response levels for less serious effects. Well designed studies that assess less serious threshold effects following acute-duration inhalation and oral exposure to 1,1,2,2-tetrachloroethane would facilitate the development of acute-duration MRL values for 1,1,2,2-tetrachloroethane. Data for dermal exposure routes are limited, but this is not a primary route of human exposure for persons living near hazardous waste sites where 1,1,2,2-tetrachloroethane may be found.

Intermediate-Duration Exposure. Reports of intermediate-duration exposures to humans by the inhalation and oral routes have been somewhat anecdotal and dated, and their interpretations complicated by uncertainties in levels of exposure to 1,1,2,2-tetrachloroethane and other chemicals (Jeney et al. 1957; Koelsch 1915; Lobo-Mendonca 1963; Minot and Smith 1921; Parmenter 1921; Willcox et al. 1915). Though mostly qualitative, these studies have confirmed that the same organ systems are affected as those for acute-duration exposure.

Intermediate-duration inhalation exposure of animals to intermittent high concentrations of 1,1,2,2-tetrachloroethane caused mortality and neurological and liver effects that are essentially acute in nature (Horiuchi et al. 1962). Information on effects of intermediate-duration inhalation exposure to lower concentrations of 1,1,2,2-tetrachloroethane is available from poorly reported studies in rats and rabbits (Kulinskaya and Verlinskaya 1972; Union Carbide Corporation 1947; Schmidt et al. 1972; Shmuter 1977; Truffert et al. 1977). These studies provide information on hepatic, reproductive, and other non-neurological effects. With the exception of the reproductive effects (Schmidt et al. 1972), these studies are inadequate for identifying a NOAEL or LOAEL due to insufficient data on incidence, magnitude, and/or severity of effects.

Intermediate-duration oral toxicity studies of 1,1,2,2-tetrachloroethane include a 21-day gavage study in rats (NTP 1996), a 16-day gavage study in mice (NTP 1993d), 6-week gavage studies in rats and mice (NCI 1978), and 15-day diet studies in rats and mice (NTP 2004a). These studies are mainly dose range-finding studies that used small numbers of animals and had limited or no evaluations of clinical chemistry and histology. Additional information on the intermediate-duration oral toxicity of 1,1,2,2-tetrachloroethane is available from comprehensive 14-week dietary studies in rats and mice (NTP 2004a) that tested wider ranges of doses and varieties of end points than the studies summarized above. The NTP (2004a) study in rats found liver-related serum chemistry changes at 80 mg/kg/day and hepatocellular necrosis at 170 mg/kg/day (NTP 2004a). Mice exposed for 14 weeks in the diet had similar liver effects at higher doses than the rats (NTP 2004a). Comprehensive neurological testing in the 14-week studies showed no effects in either species, indicating that the liver was more sensitive than the nervous system for intermediate-duration dietary exposure. The NTP (2004a) study in rats served as the basis for deriving an intermediate-duration oral MRL for 1,1,2,2-tetrachloroethane, as described in detail in Chapter 2 and Appendix A.

Additional intermediate-duration oral studies are not necessary at this time. An intermediate-duration inhalation study in laboratory animals could be designed to provide information necessary to derive an intermediate-duration inhalation MRL for 1,1,2,2-tetrachloroethane.

Chronic-Duration Exposure and Cancer. Information on the chronic inhalation toxicity of 1,1,2,2-tetrachloroethane in humans is available from several occupational studies (Jeney et al. 1957; Lobo-Mendonca 1963; Minot and Smith 1921; Norman et al. 1981) that are inadequate for identification of effect levels due to limitations that include insufficient characterization of exposure levels, lack of control data, dermal exposures, and/or mixed chemical exposures. Although not sufficient for identification of effect levels or MRL derivation, the occupational studies provide limited supporting information on the neurotoxicity and hepatotoxicity of 1,1,2,2-tetrachloroethane. Chronic inhalation studies in animals have not been performed.

The systemic effects of long-term repetitive oral exposure of mice and rats to 1,1,2,2-tetrachloroethane have been studied via gavage using several dose levels (NCI 1978). The NCI (1978) study identified LOAELs of 108 mg/kg/day for liver lesions in rats and a serious LOAEL of 284 mg/kg/day for lethal kidney lesions and reduced survival in mice. Derivation of a chronic oral MRL is precluded because lower LOAELs are identified in the more comprehensive and sensitive 14-week diet study in these species (NTP 2004a) used to derive the intermediate-duration MRL.

There is one study on the possible carcinogenic effect of 1,1,2,2-tetrachloroethane on humans via inhalation exposure (Norman et al. 1981), and there are oral studies of the effects on rats and mice (NCI 1978). The human study was inconclusive and in the NCI (1978) study, liver tumors were found in mice after long-term oral exposure. Although this species has a high rate of spontaneous incidence of these tumors, the results in the mice are indicative of a potential carcinogenic risk in humans.

There are no studies of the effect of chronic-duration dermal administration of 1,1,2,2-tetrachloroethane in humans or animals. Determination of the effect of chronic-duration dermal administration of 1,1,2,2-tetrachloroethane to animals would be methodologically problematic due to inadvertent oral and/or inhalation exposures. Additionally, chronic-duration dermal exposure is unlikely for humans. Therefore, chronic-duration studies by this route are not recommended.

Since humans are most likely to be exposed via the inhalation or oral routes, long-term animal studies that include a range of exposure levels for inhalation and oral exposure should be designed to better assess cancer and noncancer end points. Such studies would provide support to existing oral cancer data and facilitate derivation of an inhalation unit risk as well as chronic-duration inhalation and oral MRLs for 1,1,2,2-tetrachloroethane.

Genotoxicity. Information on the *in vivo* genotoxic effects of 1,1,2,2-tetrachloroethane is lacking for humans and limited for animals (see Table 3-4), although there are a number of *in vitro* tests of the mutagenicity of 1,1,2,2-tetrachloroethane (see Table 3-3). This type of data is not sufficient to determine if 1,1,2,2-tetrachloroethane is genotoxic in humans. *In vivo* testing and *in vitro* testing on human cell lines would help determine if 1,1,2,2-tetrachloroethane is genotoxic in humans. The known metabolism of 1,1,2,2-tetrachloroethane to reactive acid chlorides and/or free radical products suggests that genotoxic effects in humans and other mammals are possible. Based on observations of the mixed nature of results from available *in vivo* and *in vitro* genotoxicity tests and carcinogenicity bioassays and positive DNA binding data, additional well-designed genotoxicity testing is warranted.

Reproductive Toxicity. There were no human reproductive toxicity studies reported for 1,1,2,2-tetrachloroethane. The reproductive toxicity of 1,1,2,2-tetrachloroethane has not been adequately evaluated in animals because reproductive toxicity has not adequately been assessed using standard multiple-generation reproductive toxicity studies. After acute-duration inhalation exposure at 6,310 ppm, no effects on the testes, epididymes, ovaries, or uteruses were found in rats (NIOSH 1978). Similarly, an

intermediate-duration study by inhalation (Horiuchi et al. 1962) reported no effects on the testes in one monkey. Inhalation exposure to 1.9 ppm for 4 hours/day for 9 months had no reproductive effects in male mice; when mated with unexposed females, there were no significant changes in percentage of females having offspring, littering times, or offspring numbers, sex ratio, birth weight, or postnatal survival (Schmidt et al. 1972). The effect of oral exposure on male or female reproductive function has not been tested. Male rats that were exposed to 1,1,2,2-tetrachloroethane in the diet for 14 weeks had no adverse changes in sperm number or motility at 80 mg/kg/day (highest tested dose), although minimal to moderate atrophy of the testicular germinal epithelium, prostate gland, and seminal vesicle occurred at 320 mg/kg/day (NTP 2004a). Reproductive effects in similarly exposed female rats included estrus alterations and minimal to mild uterine atrophy at 170 mg/kg/day, and clitoral gland atrophy and ovarian interstitial cell cytoplasmic alterations at 320 mg/kg/day (NTP 2004a). Body weight loss at 320 mg/kg/day and reduced body weight gain at lower dose levels could have contributed to the effects observed in the male and female rats. There were no clear effects on histology of male or female reproductive tissues, sperm indices, or estrus cycle in mice exposed to dietary doses as high as 1,360–1,400 mg/kg/day for 14 weeks (NTP 2004a). Chronic-duration oral administration of 1,1,2,2-tetrachloroethane to rats and mice caused no increase in histological alterations in reproductive organs (NCI 1978). Due to apparently equivocal results from studies that examined various aspects of reproductive endpoints in 1,1,2,2-tetrachloroethane-exposed animals, and the lack of information regarding possible reproductive toxicity in humans, a well designed multiple-generation reproductive toxicity study in laboratory animals is needed to adequately assess the potential for 1,1,2,2-tetrachloroethane-induced reproductive toxicity.

Developmental Toxicity. The developmental toxicity of 1,1,2,2-tetrachloroethane has not been adequately assessed. Information regarding the potential for 1,1,2,2-tetrachloroethane-induced developmental toxicity following inhalation or oral exposure is restricted to a single rat study by the inhalation exposure route (Schmidt et al. 1972) and one set of rat (NTP 1991a) and mouse (NTP 1991b) studies using oral administration. In the inhalation study, male rats were exposed to 1,1,2,2-tetrachloroethane and mated with unexposed females, and the F_1 generation was observed for 12 weeks. No effects on the number of offspring per litter, neonatal body weight, offspring viability, or sex ratios were observed. No gross malformations in offspring were detected (Schmidt et al. 1972). In the oral (dietary) rat study, completely resorbed litters and significantly decreased fetal weights were reported (NTP 1991a). However, because the oral treatment also resulted in dose-related significantly reduced food consumption and serious maternal body weight effects, a direct treatment-related developmental effect could not be discerned. Fetuses were not examined for malformations. In the oral (dietary) mouse study (NTP 1991b), the lowest exposure level (0.5% in the food; dose of approximately 987 mg/kg/day)

resulted in 14% decreased maternal body weight gain during the treatment period, but there were no indications of developmental effects with respect to number of implantation sites, number of resorptions, numbers of dead and live fetuses, or gravid uterine weight. Exposure at higher levels resulted in maternal death, precluding assessment of treatment-related developmental toxicity at the higher doses.

Additional well-designed developmental toxicity studies that include comprehensive assessment of developmental toxicity end points at exposure levels below those resulting in serious maternal toxicity are needed to provide a better understanding of the potential developmental toxicity of 1,1,2,2-tetrachloroethane.

Immunotoxicity. There is a lack of useful information on the effects of 1,1,2,2-tetrachloroethane on the immune system in humans, and the information available from animal studies in this area is very limited. The human studies were dated, lacked information on the dose received and duration of exposure, and reported only gross effects on the appearance of the spleen following acute ingestion (Coyer 1944; Elliott 1933; Hepple 1927). No histopathological changes were noted in the spleens of rats that inhaled 100 ppm 1,1,2,2-tetrachloroethane for 6 hours (Deguchi 1972). In a 14-week dietary study of rats, pigmentation of the spleen was increased in males receiving 1,1,2,2-tetrachloroethane at doses ≥80 mg/kg/day and in females receiving doses ≥170 mg/kg/day; high incidences (70–100%) of atrophy in the spleen (red pulp and lymphoid follicle) of both sexes were noted at 320 mg/kg/day (NTP 2004a). No gross or histological alterations were seen in the spleen or lymph nodes of rats and mice exposed to 1,1,2,2-tetrachloroethane at doses up to 284 mg/kg/day for 78 weeks. Rabbits intermittently exposed to 1.5 ppm of 1,1,2,2-tetrachloroethane vapor for 8 months and then immunized with a typhoid vaccine showed a decrease in titers and an increase in the electrophoretic mobility of the specific antibodies (Shmuter 1977); however, these results are considered of questionable toxicological significance and study details were poorly reported. Since immunological end points are known to be very sensitive indicators of the toxicity of many chemicals, a battery of immunological function tests in animals would be helpful in clarifying whether 1,1,2,2-tetrachloroethane is an immunotoxicant.

There are no data on sensitization as a result of exposure to 1,1,2,2-tetrachloroethane by any route in humans or animals. Dermal sensitization tests in animals may be useful based on potential for dermal exposure from soil and water near hazardous waste sites.

Neurotoxicity. Information on the neurotoxicity of acute inhalation exposure to 1,1,2,2-tetrachloroethane in humans comes from a poorly reported experimental study in which two volunteers self-inhaled

various concentrations of the chemical for up to 30 minutes (Lehmann and Schmidt-Kehl 1936). The results of this study suggest that 3 ppm was the odor detection threshold, 13 ppm was tolerated without effect for 10 minutes, and 146 ppm for 30 minutes or 336 ppm for 10 minutes caused irritation of the mucous membranes, pressure in the head, vertigo, and fatigue. Other early human reports similarly found that clinical signs of high-dose acute inhalation exposure to 1,1,2,2-tetrachloroethane include drowsiness, nausea, headache, and weakness, and at extremely high concentrations, unconsciousness and respiratory failure (Coyer 1944; Hamilton 1917). In animals, signs of acute central nervous system toxicity (e.g., incoordination, loss of reflexes, labored respiration, prostration, and loss of consciousness) typically proceeded death, which occurred at concentrations of 1,000–1,253 ppm for 4–6 hours in rats (Carpenter et al. 1949; Schmidt et al. 1980b), 1,168–5,900 ppm for 1.5–3 hours in mice (Horiuchi et al. 1962; Pantelitsch 1933), and 5,050–6,310 ppm for 30 minutes in rats and guinea pigs (NIOSH 1978). Exposure to 576 ppm for 30 minutes caused reduced activity and alertness in rats and guinea pigs (NIOSH 1978). The effective concentration for a 50% decrease in spontaneous motor activity in rats was 360 ppm for a 6-hour exposure (Horvath and Frantik 1973). Intermediate-duration inhalation exposure to intermittent high concentrations of 1,1,2,2-tetrachloroethane caused neurological effects that are essentially acute in nature. Rats that were exposed to 9,000 ppm for 2 hours/day 2–3 times/week for 29 days became hyperactive within the first few minutes of each exposure, followed by ataxic gait within approximately 20 minutes and eventual near-complete loss of consciousness within 1–1.5 hours (Horiuchi et al. 1962). A monkey that was exposed to 1,974 ppm for 2 hours/day, 6 days/week for 190 exposures in 9 months developed, beginning at the fifteenth exposure, near-complete unconsciousness for 20–60 minutes after each exposure (Horiuchi et al. 1962).

Information on the neurotoxicity of oral exposure to 1,1,2,2-tetrachloroethane in humans is available from several case reports. People who intentionally ingested lethal amounts usually lost consciousness within approximately 1 hour and died 3–20 hours postingestion (Elliott 1933; Forbes 1943; Hepple 1927; Lilliman 1949; Mant 1953; Sherman 1953). No deaths occurred in 11 patients who were accidentally given an estimated oral dose of 68–118 mg/kg as medicinal treatment for hookworm, although they experienced loss of consciousness and other clinical signs of narcosis that included shallow breathing, faint pulse, and pronounced lowering of blood pressure (Sherman 1953; Ward 1955). In animals, lethargy and central nervous system depression occurred in rats gavaged with 270–300 mg/kg/day for 1–12 days (Hanley et al. 1988; NTP 1993a, 1993b) or 208 mg/kg/day for 21 days (NTP 1996). Information on neurological effects of lower acute oral doses is limited to a poorly reported rat study in which a single gavage dose of 100 mg/kg caused ataxia and 50 mg/kg caused decreased passive avoidance to an electric shock, possibly due to an increased threshold of shock perception due to a subtle anesthetic effect (Wolff

1978). No clinical signs of neurotoxicity were observed in 14-week dietary studies in which rats and mice were exposed to doses as high as 320 and 1,400 mg/kg/day, respectively (NTP 2004a). Comprehensive neurological evaluations (functional observational batteries) in the 14-week studies showed no effects in either species, although 80 mg/kg/day was the highest tested dose in the rats.

Tests to show the site of action would be helpful in determining exactly how 1,1,2,2-tetrachloroethane affects the nervous system of humans.

Epidemiological and Human Dosimetry Studies. Available epidemiological data are restricted to a limited report in which the cancer mortality of service men exposed to 1,1,2,2-tetrachloroethane during World War II was assessed (Norman et al. 1981). The exposure was presumed to be mostly by inhalation, but dermal exposure was also possible and precise dosimetry was unknown. Over 1,000 subjects were used in each of the control and exposed groups. There were only very slightly elevated incidences (not statistically significant) of cancer of the genital organs, as well as leukemia and lymphoma. Because environmental levels of 1,1,2,2-tetrachloroethane measured in the United States are relatively low (<10 ppt in ambient air and <25 ppb in water), exposure of the general population is expected to be very low. It is possible that humans who live near hazardous waste sites or facilities that produce or use 1,1,2,2-tetrachloroethane may be exposed to higher levels of this substance in the air, water, and soil. If populations with higher levels of exposure to 1,1,2,2-tetrachloroethane are identified, epidemiological and biomonitoring studies should be conducted to assess exposure levels and neurological, liver, and kidney effects, as well as potential reproductive, developmental, and cancer endpoints, with particular emphasis on effects of chronic-duration low-level exposures.

Biomarkers of Exposure and Effect.

Exposure. Since the metabolites of 1,1,2,2-tetrachloroethane are known, and can be measured in the urine of rats (Yllner 1971), it is possible to measure these metabolites in urine to see if a person has been exposed to 1,1,2,2-tetrachloroethane. However, these metabolites are common to several types of chlorinated ethanes and would not be specific for exposure to 1,1,2,2-tetrachloroethane. Also, 1,1,2,2-tetrachloroethane is metabolized and excreted rather quickly, and the test might only indicate whether the person had been exposed in the last few days. It would be useful to ascertain if measurements of parent compounds and metabolites in excreta or in biopsy samples (e.g., adipose) could be used to quantitate the body burden associated with exposures to known concentrations of 1,1,2,2-tetrachloroethane.

Effect. 1,1,2,2-Tetrachloroethane may cause liver damage. In cases where humans have been exposed to high levels of 1,1,2,2-tetrachloroethane, it may be possible to correlate urinary metabolites with serum indicators of liver malfunction. Although this is a data need, the metabolites would not be specific for 1,1,2,2-tetrachloroethane.

Absorption, Distribution, Metabolism, and Excretion. In both humans (Lehmann and Schmidt-Kehl 1936; Morgan et al. 1970) and laboratory animals (Hanley et al. 1988), 1,1,2,2-tetrachloroethane is well absorbed after acute-duration inhalation exposure. While studies in which the quantitation of absorption following oral exposure was measured in humans were not available, the profound effects following ingestion of 1,1,2,2-tetrachloroethane indicate that appreciable amounts are absorbed by this route also. This is consistent with the data from animal studies, which indicate that oral doses are mostly absorbed (Milman et al. 1984; Mitoma et al. 1985). No studies were located regarding absorption following dermal exposure in humans. Only limited information was found regarding the distribution of 1,1,2,2-tetrachloroethane following inhalation, oral, or dermal exposure in humans and animals. High levels of binding of 1,1,2,2-tetrachloroethane equivalents to hepatic proteins were found in rats and mice following oral dosing. 1,1,2,2-Tetrachloroethane is extensively metabolized in animals and excreted chiefly as metabolites in urine and breath (Ikeda and Ohtsuji 1972; Mitoma et al. 1985; Yllner 1971).

Modern techniques employing mass spectrometry and/or nuclear magnetic resonance coupled with high resolution chromatographic methods to provide unambiguous structural identification were used only in a few recent studies. Unfortunately, the emphasis in those studies was the elucidation of particular mechanisms of reactive intermediate metabolite formation. A more broadly based evaluation of the formation of nontoxic or less toxic metabolites was not fully pursued. Fuller studies, such as that of Yllner (1971), employed less rigorous characterization methodology and structural assignments of metabolites made are not definitive. Metabolic pathways, and rates and patterns of distribution and excretion may be different following oral exposure than following inhalation or dermal exposure. Differences in metabolism may account for differences in toxicity following exposure by these routes. Thus, further studies in animals of the rate and extent of absorption and excretion, of distribution, and of metabolism following exposure by all three routes, and *in vitro* studies to elucidate metabolic pathways, would provide the information to fully characterize the pharmacokinetics of 1,1,2,2-tetrachloroethane in animals.

Comparative Toxicokinetics. PBPK modeling of the kinetics of 1,1,2,2-tetrachloroethane in rats exposed by inhalation has been performed by Gargas and Andersen (1989). Data on comparative toxicokinetics in rats and mice exposed to 1,1,2,2-tetrachloroethane by intermediate-duration inhalation exposure are available (Mitoma et al. 1985). Mice metabolized 1,1,2,2-tetrachloroethane at roughly twice the rate of rats given similar doses, and the amount of protein bound equivalents were higher. Further studies in these and other species may provide information to account for differences in toxicity among animal species. There are limited human metabolism and excretion data. A single study has shown that 3% of inhaled 1,1,2,2-tetrachloroethane was excreted in the breath, and that the urinary excretion rate was 0.015% absorbed dose/minute (Morgan et al. 1970). Analysis of levels of metabolites in the urine of people with known exposure is a data need that could provide knowledge of metabolic pathways in humans. Additionally, biochemically viable human tissues, including liver, are now routinely available for metabolism studies. In this way, the metabolism of 1,1,2,2-tetrachloroethane in humans of differing genetic background and life style (e.g., consumers of alcohol or tobacco) can be determined in microsomes and precision-cut tissue slices. This information may allow accurate prediction of the metabolism of 1,1,2,2-tetrachloroethane in humans. Qualitative comparisons of human metabolites with those of animals could help to fill a data need by identifying the most appropriate animal species to serve as a model for predicting toxic effects in humans and studying the mechanism of action. PBPK models could be developed and used to estimate 1,1,2,2-tetrachloroethane target tissue levels following environmentally-relevant exposures. These PBPK models would be useful tools for dose-response health assessments.

Methods for Reducing Toxic Effects. No studies were located regarding the mechanism of absorption in humans or animals after inhalation, oral, or dermal exposure to 1,1,2,2-tetrachloroethane. Carbon and castor oil have been shown to increase the survival times in rats administered oral doses of 1,1,2,2-tetrachloroethane (Laass 1973a, 1973b, 1974a, 1974b), but data are needed on the actual mechanisms of absorption and distribution of this chemical in the body. 1,1,2,2-Tetrachloroethane is metabolized to reactive toxic acyl chlorides and to free radicals. No treatments were described that mitigate the health effects that result from exposure to the compound. However, alcohol and acetone, inducers of cytochrome P-450 isoenzyme 2E1 increased the metabolism of 1,1,2,2-tetrachloroethane and intensified the toxic effects (Gohlke and Schmidt 1972; Sato et al. 1980). Studies to determine methods for blocking the absorption or increasing the excretion of 1,1,2,2-tetrachloroethane would be helpful to better define methods to reduce the toxic effects of the chemical.

Children's Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

No information was located regarding potential age-related differences in susceptibility to 1,1,2,2-tetrachloroethane in humans or animals. A well-designed animal study would provide valuable information regarding the potential for age-related susceptibility to 1,1,2,2-tetrachloroethane. Such a study could be designed to assess developmental neurotoxicity since the nervous system is one of the known targets of 1,1,2,2-tetrachloroethane toxicity.

Child health data needs relating to exposure are discussed in Section 6.8.1, Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

No ongoing studies pertaining to 1,1,2,2-tetrachloroethane were located in a search of the Federal Research in Progress database (FEDRIP 2006).

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4. CHEMICAL AND PHYSICAL INFORMATION

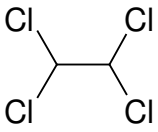
4.1 CHEMICAL IDENTITY

Information regarding the chemical identity of 1,1,2,2-tetrachloroethane is located in Table 4-1.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of 1,1,2,2-tetrachloroethane is located in Table 4-2.

Table 4-1. Chemical Identity of 1,1,2,2-Tetrachloroethane

Characteristics	Information	References
Chemical name	1,1,2,2-Tetrachloroethane	Lide 2005
Synonyms	Tetrachloroethane; acetylene tetrachloride; dichloro-2,2-dichloroethane; s-tetrachloroethane	ChemID 2004
Trade names	Bonoform, Cellon, Westron, Acetosol	ChemID 2004; HSDB 2006
Chemical formula	$C_2H_2Cl_4$	O'Neil et al. 2001
Chemical structure		Lide 2005
Identification numbers:		
CAS registry	79-34-5	ChemID 2004
NIOSH RTECS	KI8575000	RTECS 2006
EPA hazardous waste	U209	RTECS 2006
OHM/TADS	8100014	HSDB 1995
DOT/UN/NA/IMDG shipping	UN 1702; IMDG 6.1	HSDB 2006
HSDB	123	HSDB 2006
NCI	NCI-C03554	RTECS 2006

CAS = Chemical Abstracts Service; DOT/UN/NA/IMDG -Department of Transportation/United Nations/North America/ Intergovernmental Maritime Consultive Organization; EPA = Environmental Protection Agency; HSDB = Hazardous Substance Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data Base; RTECS = Registry of Toxic Effects of Chemical Substances

Table 4-2. Physical and Chemical Properties of 1,1,2,2-Tetrachloroethane

Property	Tetrachloroethane	References
Molecular weight	167.85	O'Neil et al. 2001
Color	Colorless	Lewis 2001
Physical state	Liquid	Lewis 2001
Melting point	-42.4 °C	O'Neil et al. 2001
Boiling point	145.2 °C	Lide 2005
Density (20 °C)	1.6	Lewis 2001
Odor	Sweetish, suffocating, chloroform-like	O'Neil et al. 2001
Odor threshold		
Water	0.5 ppm	Amoore and Hautala 1983
Air	1.5 ppm	Amoore and Hautala 1983
Solubility		
Water at 25 °C	2.83×10^3 mg/L	Horvath et al. 1999
Organic solvents	Miscible with methanol, ethanol, benzene, ether, petroleum ether, carbon tetrachloride, chloroform, carbon disulfide, dimethylformamide, oils	O'Neil et al. 2001
Partition coefficients		
Log octanol/water	2.39	Hansch et al. 1995
K_{oc}	46, 83, 118, 173, 216, 240	Borisover and Graber 1997; Chiou et al. 1979; Chu and Chan 2000; Valsaraj et al. 1999
Vapor pressure		
25 °C	4.62 mmHg	AIChE 1995
Henry's law constant		
atm/m^3-molecule at 25 °C	3.67×10^{-4} atm-m^3/mol	Leighton and Calo 1981
Conversion factors		
ppm (v/v) to mg/m^3 in air (20 °C)	1 ppm=6.98 mg/m^3	Verschueren 2001
mg/m^3 to ppm (v/v) in air (20 °C)	1 mg/m^3=0.14 ppm	Verschueren 2001
Bioconcentration factor		
BCF	8, 2	ASTER 1995; Barrows et al. 1980

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5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.1 PRODUCTION

1,1,2,2-Tetrachloroethane as an end-product was formerly produced in the United States only by the Specialty Materials Division of Eagle-Picher Industries in Lenexa, Kansas (SRI 1988). By the late 1980s, this facility had been sold to the Vulcan Materials Company, and production was discontinued at the Kansas facilities (Montgomery and Welkom 1990; SRI 1992, 1993). Approximately 440 million pounds (199.5 million kg) of 1,1,2,2-tetrachloroethane were produced in the United States in 1967 (Konietzko 1984). Production declined markedly thereafter, falling to an estimated 34 million pounds (15.4 million kg) by 1974. The production volumes of 1,1,2,2-tetrachloroethane reported by U.S. manufacturers in 1986, 1990, 1994, and 1998 have fluctuated within a range of <1 million to 50 million pounds (IUR 2002). The production volume reported in 2002 was within the range of <1 million to 10 million pounds (IUR 2002).

Commercial production of 1,1,2,2-tetrachloroethane as an end-product has apparently ceased in the United States. This parallels patterns in Canada, where the last plant to manufacture 1,1,2,2-tetrachloroethane as an end-product ceased operations by 1985 (CEPA 1993). Any remaining production in the United States or Canada at the present time would involve 1,1,2,2-tetrachloroethane generated for on-site uses as a chemical intermediate, as a trace constituent with other chemicals, or as part of a waste stream in releases to the environment.

1,1,2,2-Tetrachloroethane can be produced by the catalytic addition of chlorine to acetylene (Rossberg et al. 2005); it may also be produced by the direct chlorination or oxychlorination of ethylene or 1,2-dichloroethane (Archer 1979; Rossberg et al. 2005). In most cases, 1,1,2,2-tetrachloroethane was not isolated to form an end-product, but was immediately thermally cracked to yield desired chemicals such as trichloroethylene, tetrachloroethylene, and 1,2-dichloroethylene (Archer 1979). 1,1,2,2-Tetrachloroethane may be produced as a by-product in the manufacture of chemicals such as 1,1,1- and 1,1,2-trichloroethane (Rossberg et al. 2005). Section 5.3 summarizes information on several chemicals with which 1,1,2,2-tetrachloroethane can appear as a trace constituent.

Table 5-1 lists the facilities in each state that process 1,1,2,2-tetrachloroethane, the intended use, and the range of maximum amounts of 1,1,2,2-tetrachloroethane that are stored on site. Current production is for

Table 5-1. Facilities that Produce, Process, or Use 1,1,2,2-Tetrachloroethane

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AR	3	1,000	99,999	10, 12
CA	2	100	999,999	9, 11
CO	7	1,000	99,999	1, 2, 5, 6, 11, 12, 13
CT	1	1,000	9,999	12
FL	2	100	99,999	12
KS	3	100	9,999	1, 5, 9, 12
KY	4	10,000	9,999,999	1, 3, 5, 6
LA	29	100	49,999,999	1, 2, 3, 4, 5, 6, 12, 13
MI	2	0	99,999	5, 7, 12
MN	1	10,000	99,999	11
MO	1	1,000	9,999	12
NC	1	100,000	999,999	7
NE	2	1,000	99,999	12
NJ	2	1,000	99,999	10
NY	1	10,000	99,999	12
OH	2	1,000	999,999	7, 9, 12
PA	1	10,000	99,999	10
SC	3	10,000	99,999	2, 3, 4, 7, 9
TN	6	10,000	99,999	2, 3, 4, 7, 8, 10, 12
TX	25	0	9,999,999	1, 2, 3, 5, 6, 11, 12, 13, 14
VA	1	100	999	12
AR	3	1,000	99,999	10, 12
CA	2	100	999,999	9, 11
CO	7	1,000	99,999	1, 2, 5, 6, 11, 12, 13
CT	1	1,000	9,999	12
FL	2	100	99,999	12
KS	3	100	9,999	1, 5, 9, 12
KY	4	10,000	9,999,999	1, 3, 5, 6
LA	29	100	49,999,999	1, 2, 3, 4, 5, 6, 12, 13
MI	2	0	99,999	5, 7, 12
MN	1	10,000	99,999	11
MO	1	1,000	9,999	12
NC	1	100,000	999,999	7
NE	2	1,000	99,999	12
NJ	2	1,000	99,999	10
NY	1	10,000	99,999	12
OH	2	1,000	999,999	7, 9, 12
PA	1	10,000	99,999	10

Table 5-1. Facilities that Produce, Process, or Use 1,1,2,2-Tetrachloroethane

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
SC	3	10,000	99,999	2, 3, 4, 7, 9
TN	6	10,000	99,999	2, 3, 4, 7, 8, 10, 12
TX	25	0	9,999,999	1, 2, 3, 5, 6, 11, 12, 13, 14
VA	1	100	999	12

[a]Post office state abbreviations used
[b]Amounts on site reported by facilities in each state
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses
14. Process Impurity

Source: TRI05 2007 (Data are from 2005)

on-site uses or as a by-product, so that the phrase "manufacture" in the table heading does not imply production for sale as a commercial end-product. The data listed in Table 5-1 are derived from the Toxics Release Inventory (TRI) and refer to facilities operating in 2005 (TRI05 2007). Only certain types of facilities are legally required to report, and therefore, this is not an exhaustive list (TRI05 2007).

5.2 IMPORT/EXPORT

Limited data pertaining to the import or export of 1,1,2,2-tetrachloroethane were located in the available literature. Imports in 1982 totaled 65,500 kg (144,100 pounds) (HSDB 1996). Present tariff-setting and record-keeping practices combine 1,1,2,2-tetrachloroethane with other chemicals (USITC 1994). Total U.S. imports and exports of hexachloroethane and tetrachloroethane combined were 128,865 kg (283,503 pounds) and 11,282,409 kg (24,821,300 pounds) in 2005, respectively (U.S. Department of Commerce 2006).

5.3 USE

In the past, the major use for 1,1,2,2-tetrachloroethane was in the production of trichloroethylene, tetrachloroethylene, and 1,2-dichloroethylene (Archer 1979). It was also used as a solvent, in cleaning and degreasing metals, in paint removers, in varnishes and lacquers, in photographic films, and as an extractant for oils and fats (Lewis 2001). Although at one time, it could be used as an insecticide, fumigant, and weed killer (Lewis 2001), it presently is not registered for any of these purposes. It was once used as an ingredient in an insect repellent, but registration was canceled in the late 1970s. With the availability of less toxic solvents and the development of new processes for manufacturing chlorinated ethylenes, the manufacture of 1,1,2,2-tetrachloroethane as a commercially marketed end-product has steadily declined in the United States and now appears to have ceased (HSDB 2006). A similar trend is reported in Canada (CEPA 1993).

1,1,2,2-Tetrachloroethane can still appear as a chemical intermediate in the production of a variety of other common chemicals. Trace amounts of 1,1,2,2-tetrachloroethane may be introduced into the environment as these other chemicals are produced, or it may appear as a minor impurity in the end-products. Therefore, it is helpful to know how some of these other chemicals are related to 1,1,2,2-tetrachloroethane (e.g., CEPA 1993; Harte et al. 1991). Several of these chemicals, including trichloroethylene (TCE); 1,1,2-trichloroethane; 1,2-dichloroethene (DCE or vinylidene chloride);

tetrachloroethylene (perchloroethylene, PCE, or PERC); vinyl chloride; 1,2-dichloroethane (ethylene dichloride [EDC]); and 1,1,1-trichloromethane (methyl chloroform), are the subjects of separate ATSDR profiles, which are available through the internet (http://www.atsdr.cdc.gov/toxpro2.html).

5.4 DISPOSAL

1,1,2,2-Tetrachloroethane disposal should follow the Resource Conservation and Recovery Act (RCRA) regulations appropriate for halogenated organic compound (HOC) wastes, which are likely to contain >1,000 ppm of HOCs (EPA 2006d, 2006e). Selection of an appropriate technology for waste treatment and disposal depends on the RCRA waste code number. RCRA defines five main categories of wastes. Waste code U209 is specifically assigned to 1,1,2,2-tetrachloroethane, but wastes containing 1,1,2,2-tetrachloroethane could be assigned to one or more of 25 halogenated organic wastes under the RCRA U and P waste series.

For these U and P series wastes, the EPA has proposed three treatment technologies as alternative Best Demonstrated Available Technology (BDAT) treatment standards: (1) wet air oxidation followed by carbon adsorption; (2) chemical oxidation followed by carbon adsorption; or (3) incineration of waste waters. The BDAT for these HOC waste types is incineration. Industrial boilers or furnaces that function like waste disposal incinerators (e.g., cement kilns) may also substitute the combustible wastes for their normal fuel stocks. However, EPA does not believe that fuel substitution is a viable alterative for the majority of class U ("off-spec" materials that may contain impurities or mixtures of other wastes) HOC products. Chapter 8 of this profile provides a comprehensive overview of federal or state laws and regulations related to 1,1,2,2-tetrachloroethane.

The following categories of hazardous wastes include 1,1,2,2-tetrachloroethane as a hazardous constituent:

- process waste from the production of certain chlorinated aliphatic hydrocarbons (containing chains of one to five carbons);
- distillation light ends, spent filters, and spent desiccant generated in the production of certain chlorinated aliphatic hydrocarbons;
- wastes from the production of ethylene dichloride, vinyl chloride, trichloroethylene, perchloroethylene, chlorine, and 1,1,1-trichloroethane; and

- off-specification 1,1,2,2-tetrachloroethane (i.e., 1,1,2,2-tetrachloroethane that does not meet desired chemical purity).

Only one of these categories of wastes (process waste from the production of chlorinated aliphatic hydrocarbons) has an EPA-prescribed treatment standard before land disposal. Such wastes must be treated by incineration to comply with the restrictions. The other waste categories have concentration-based standards that must be achieved before being sent to a RCRA-permitted land disposal facility (EPA 2006e). The waste streams generated from the manufacture of vinyl chloride and ethylene dichloride have been noted in studies in both the United States and Canada to contain high levels of 1,1,2,2-tetrachloroethane (CEPA 1993). These waste streams are currently treated to recover and recycle many types of organic products prior to incineration, but trace amounts of 1,1,2,2-tetrachloroethane will remain, contributing to atmospheric emissions during the incineration disposal process, even assuming rates of destruction in excess of 99% (CEPA 1993).

6. POTENTIAL FOR HUMAN EXPOSURE

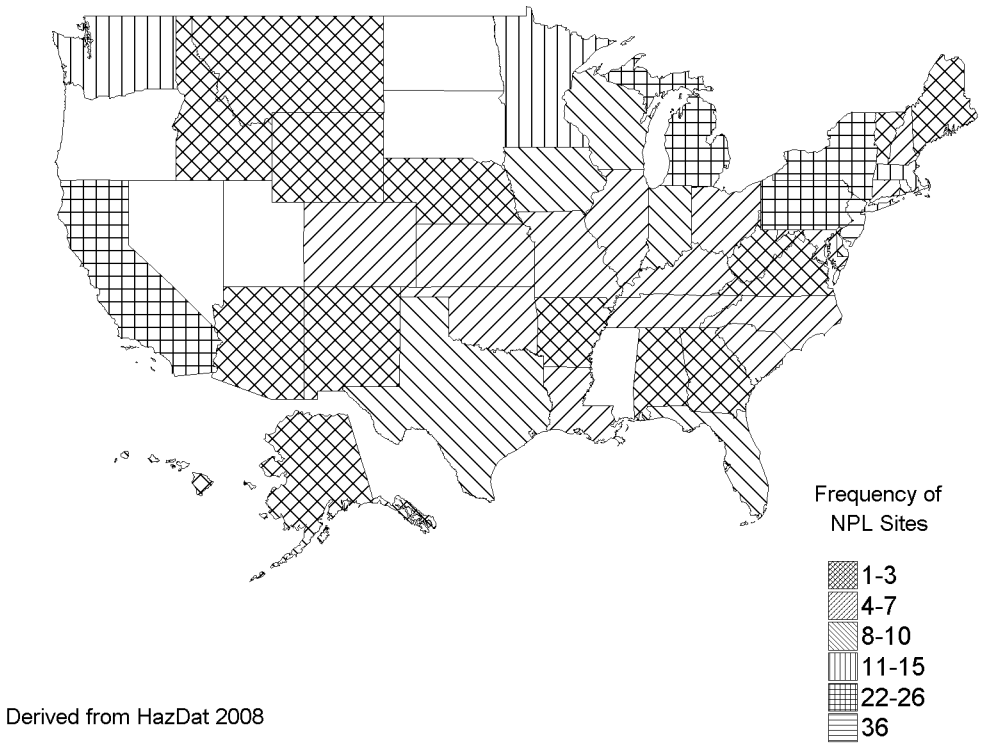
6.1 OVERVIEW

1,1,2,2-Tetrachloroethane has been identified in at least 329 of the 1,699 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2008). However, the number of sites evaluated for 1,1,2,2-tetrachloroethane is not known. The frequency of these sites can be seen in Figure 6-1.

1,1,2,2-Tetrachloroethane is a synthetic chemical and is not known to occur naturally in the environment (IARC 1979). This chemical has been used as an intermediate in the production of chlorinated ethenes, as an industrial solvent and extractant, and as an ingredient in a few pesticide preparations. Its production as an end-product declined markedly after the late 1960s, and by the early 1990s, its manufacture as an end-product had ceased both in the United States and in Canada (CEPA 1993). Therefore, current releases of 1,1,2,2-tetrachloroethane are limited to fugitive emissions or discharges during its production and use as a chemical intermediate or during its formation as a byproduct.

1,1,2,2-tetrachloroethane is released primarily to the atmosphere and to surface water; very small amounts are now being land-applied. If released onto soil, some of the chemical would be expected to volatilize, with the remainder leaching into the subsurface soil profile and, possibly, into groundwater. 1,1,2,2-Tetrachloroethane is not expected to adsorb to soils and sediments based on measured K_{oc} values ranging from 46 to 240 (Borisover and Graber 1997; Chiou et al. 1979; Chu and Chan 2000; Swann et al. 1983; Valsaraj et al. 1999). If 1,1,2,2-tetrachloroethane is released to surface water, most of it would volatilize based on estimated volatilization half-lives of 6.9 hours to 6.1 days (Leighton and Calo 1981; Thomas 1990), with the remainder dissolving in water where it would undergo degradation through hydrolysis. In groundwater, the major degradation processes involve anaerobic biodegradation and chemical hydrolysis. Chemical hydrolysis is very sensitive to pH and is much faster under basic or neutral conditions. 1,1,2,2-Trichloroethylene is the primary metabolite of chemical hydrolysis. Measured half-lives for the chemical hydrolysis of 1,1,2,2-tetrachloroethane at neutral pHs range from 29 to 102 days. Anaerobic biodegradation proceeds by hydrogenolysis, dichloroelimination, or dehydrochlorination; products of biodegradation include 1,2-dichloroethylene, 1,1,2-trichloroethane, 1,2-dichloroethane, and the highly toxic vinyl chloride. Bioconcentration of this substance in aquatic organisms is

Figure 6-1. Frequency of NPL Sites with 1,1,2,2-Tetrachloroethane Contamination



expected to be low based on measured BCF values of 2 and 8 (ASTER 1995; Barrows et al. 1980; Franke et al. 1994).

In the atmosphere, 1,1,2,2-tetrachloroethane is removed primarily via reaction with photochemically generated hydroxyl radicals. The half-life of this reaction is 54 days, calculated using a measured rate constant (Tosato et al. 1991). Atmospheric removal may also occur through washout by precipitation; however, most 1,1,2,2-tetrachloroethane removed by this mechanism will likely reenter the atmosphere by volatilization. Slow diffusion into the stratosphere will also occur, where 1,1,2,2-tetrachloroethane may participate in reactions that generate ozone-destroying chlorine radicals. However, this chemical is not expected to contribute significantly to the destruction of the ozone layer since <1% of the tropospheric 1,1,2,2-tetrachloroethane is expected to reach the stratosphere (EPA 1979; WHO 1998).

Reported average concentrations of 1,1,2,2-tetrachloroethane measured in ambient air from both urban and rural locations across the United States are generally <10 ppt (Brodzinsky and Singh 1982; Class and Ballschmiter 1986; EPA 1988c; Pratt et al. 2000). However, average urban air concentrations as high as 57 ppb have been reported (Harkov et al. 1981, 1983; Lioy et al. 1985; Singh et al. 1981, 1982). 1,1,2,2-Tetrachloroethane was detected in approximately 43% of 12,476 water samples (surface water and groundwater) listed in the STORET database (EPA 2006f). However, only 3% of the samples contained 1,1,2,2-tetrachloroethane above the quantitation limit (unspecified). The range, mean, and median of quantifiable 1,1,2,2-tetrachloroethane concentrations were 0.1–25, 0.6, and 0.5 ppb, respectively. 1,1,2,2-Tetrachloroethane was detected in <0.001% of 166,559 public water system samples collected in the United States between 1993 and 1997 (EPA 2001b). Limited monitoring data are available for 1,1,2,2-tetrachloroethane in soil or sediment. The existing data indicate that this substance is not widely detected in these media (EPA 2006f; Krill and Sonzogni 1986; Shilling 1985; Westrick et al. 1984). 1,1,2,2-Tetrachloroethane has not been detected in table-ready foods (FDA 2005b).

Based on the low levels of 1,1,2,2-tetrachloroethane measured in the environment and the decreased use of this substance in nonindustrial settings, exposure of the general population to 1,1,2,2-tetrachloroethane is expected to be very low. However, individuals located near hazardous waste sites or facilities where 1,1,2,2-tetrachloroethane is used as a chemical intermediate may be exposed to this substance by inhalation of contaminated air, by ingestion of contaminated drinking water, or by dermal contact with contaminated soil. Occupational exposures are expected to occur primarily via inhalation and dermal contact.

6.2 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ 10 or more full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005).

6.2.1 Air

Estimated releases of 3,170 pounds (1.4 metric tons) of 1,1,2,2-tetrachloroethane to the atmosphere from 20 domestic manufacturing and processing facilities in 2005, accounted for about 90% of the estimated total environmental releases from facilities required to report to the TRI (TRI05 2007). These releases are summarized in Table 6-1.

1,1,2,2-Tetrachloroethane is expected to be released into the air during the process of manufacturing trichloroethylene and other chlorinated hydrocarbons (WHO 1998). It may also be emitted from hazardous waste landfills (Harkov et al. 1987). In the past, 1,1,2,2-tetrachloroethane may have been released to the air during its use as a metal degreasing agent; as a paint, varnish, and rust remover; and as an extractant, solvent, and chemical intermediate (Lewis 2001). However, these are no longer expected to be important sources of release since the use of 1,1,2,2-tetrachloroethane as an end-product appears to have ceased in the United States.

1,1,2,2-Tetrachloroethane was one of the 10 most prevalent chlorinated chemicals found in solvent wastes that were incinerated each year prior to 1980 (Travis et al. 1986). A study was performed to ascertain the annual emissions of these chlorinated chemicals from a hypothetical 4,400 kw rotary kiln incinerator,

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use 1,1,2,2-Tetrachloroethane[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AR	1	54	No data	0	0	0	54	0	54
CO	1	0	No data	0	0	0	0	0	0
KY	1	122	0	0	0	0	122	0	122
LA	8	1,986	5	0	35	0	1,991	35	2,026
NY	1	0	No data	0	No data	0	No data	0	0
OH	1	5	0	0	255	0	5	255	260
SC	1	0	No data	0	0	0	0	0	0
TX	6	1,003	1	0	18	0	1,022	0	1,022
Total	20	3,170	6	0	308	0	3,194	290	3,484

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other on-site landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI05 2007 (Data are from 2005)

with each chemical being represented according to its fraction in the stack of the incinerator. Annual stack emissions of 1,1,2,2-tetrachloroethane from such an incinerator were estimated to be 7.1 kg, assuming a standard destruction and removal efficiency of 99.99% and a waste throughput of $2.76x10^7$ kg/year. Current information on incinerator-related generation of 1,1,2,2-tetrachloroethane could not be identified. Tam and Neumann (2004) reported that 607 pounds of 1,1,2,2-tetrachloroethane were emitted into the air in Portland, Oregon during 1996.

1,1,2,2-Tetrachloroethane has been identified in air samples collected at 20 of the 1,699 NPL hazardous waste sites where it was detected in some environmental media (HazDat 2008).

6.2.2 Water

Estimated releases of 6 pounds (0.002 metric tons) of 1,1,2,2-tetrachloroethane to surface water from 20 domestic manufacturing and processing facilities in 2005, accounted for <1% of the estimated total environmental releases from facilities required to report to the TRI (TRI05 2007). These releases are summarized in Table 6-1.

1,1,2,2-Tetrachloroethane may be released into water through effluent from manufacturing facilities that use this substance as a chemical intermediate. Though no longer representing current conditions, a comprehensive waste water survey conducted by the Effluent Guidelines Division of the EPA (Shackelford et al. 1983) documented that 1,1,2,2-tetrachloroethane has been detected in a variety of waste water discharges. Approximately 4,000 samples of waste water from a broad range of industrial facilities and publicly owned treatment works (POTWs) were analyzed in this survey.

1,1,2,2-Tetrachloroethane has been identified in groundwater and surface water samples collected at 218 and 43 of the 1,699 NPL hazardous waste sites, respectively, where it was detected in some environmental media (HazDat 2008).

6.2.3 Soil

Estimated releases of 308 pounds (0.1 metric tons) of 1,1,2,2-tetrachloroethane to soils from 20 domestic manufacturing and processing facilities in 2005, accounted for about 9% of the estimated total

environmental releases from facilities required to report to the TRI (TRI05 2007). These releases are summarized in Table 6-1.

1,1,2,2-Tetrachloroethane may be released to soil when it is disposed of in landfills. Another possible mode of release to soil is from accidental spills of products or wastes containing 1,1,2,2-tetrachloroethane during overland transportation.

1,1,2,2-Tetrachloroethane has been identified in soil and sediment samples collected at 112 and 22 of the 1,699 NPL hazardous waste sites, respectively, where it was detected in some environmental media (HazDat 2008).

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

Most of the 1,1,2,2-tetrachloroethane that is released to the environment enters the atmosphere, where it is expected to be degraded by reaction with photochemically produced hydroxyl radicals. The half-life for this reaction is approximately 54 days based on a measured rate constant of 2.50×10^{-13} cm^3/molecule-second (Tosato et al. 1991). 1,1,2,2-Tetrachloroethane that is not degraded in the troposphere may be transported to the stratosphere by processes such as diffusion, where it will then photodegrade rapidly. However, based on an estimated half-life and a tropospheric-to-stratospheric turnover time of 30 years (EPA 1979), it has been predicted that <1% of tropospheric 1,1,2,2-tetrachloroethane would eventually reach the stratosphere. Removal of 1,1,2,2-tetrachloroethane from the atmosphere may also occur through washout by precipitation; however, most 1,1,2,2-tetrachloroethane removed by this mechanism will likely reenter the atmosphere by volatilization.

1,1,2,2-Tetrachloroethane that is released into surface water will be lost by volatilization in a period of days to weeks. Based on a measured Henry's law constant of 3.67×10^{-4} atm-m^3/mol (Leighton and Calo 1981), the volatilization half-life of 1,1,2,2-tetrachloroethane (assuming first-order decay kinetics) is estimated to be 6.9 hours from a model river 1 m deep flowing 1 m/second with a wind of 3 m/second and 6.1 days from a model lake 1 m deep flowing 0.05 m/second with a wind of 0.5 m/second (Thomas 1990). In waste water treatment plants that receive volatile compounds such as 1,1,2,2-tetrachloroethane from industrial discharges or other sources, air stripping is an important mechanism for transferring the chemical from the water into the air. Air stripping technologies involve cascading waste waters over

trickling towers, the use of spray devices to convert the fluids into droplets or aerosols, and other techniques to increase the ordinary volatilization processes across liquid surfaces. In stripping, as opposed to ordinary volatilization, the liquid and gas phases are dispersed. As a result, the interfacial surface area is much greater and liquid/gas mass transfer is greatly enhanced. Stripping, not biodegradation, was found to be responsible for removing 96% of the 1,1,2,2-tetrachloroethane in tests performed with activated sludge reactors (Kincannon et al. 1983). The half-disappearance time for 1,1,2,2-tetrachloroethane removal by stripping was 0.3 hours. In view of its moderate vapor pressure and low adsorptivity to soil, 1,1,2,2-tetrachloroethane would be expected to readily volatilize from soil surfaces. However, 1,1,2,2-tetrachloroethane may also leach into groundwater as indicated by its presence in aquifer discharge (Lorah and Voytek 2004).

The K_{oc} of 1,1,2,2-tetrachloroethane is 46 in a silt loam soil (Chiou et al. 1979). Valsaraj et al. (1999) reported K_{oc} values of 240, 216, and 173 for 1,1,2,2-tetrachloroethane in sandy soil (0.11% organic carbon), clay soil (0.25% organic carbon), and silty clay soil (1.13% organic carbon), respectively. K_{oc} values of 118 and 83 have also been reported (Borisover and Graber 1997; Chu and Chan 2000). These K_{oc} values suggests that 1,1,2,2-tetrachloroethane will not adsorb appreciably to soil, suspended solids, and sediment (Swann et al. 1983).

The bioconcentration factor (BCF) of 1,1,2,2-tetrachloroethane measured in bluegill sunfish was 8 in a 14-day experiment (Barrows et al. 1980). A bioconcentration factor of 2 for 1,1,2,2-tetrachloroethane in fathead minnows has also been reported (ASTER 1995). According to a classification scheme, these BCF values suggest that the potential for bioconcentration of 1,1,2,2-tetrachloroethane in aquatic organisms is low (Franke et al. 1994).

6.3.2 Transformation and Degradation

6.3.2.1 Air

The primary reaction of 1,1,2,2-tetrachloroethane in the atmosphere is expected to be with photo-chemically produced hydroxyl radicals. Based on a measured rate constant of 2.50×10^{-13} cm^3/molecule-seconds at 25 °C and a hydroxyl radical concentration of 5.00×10^5 molecules/cm^3, the half-life for this reaction is 64 days (Tosato et al. 1991). 1,1,2,2-Tetrachloroethane that reaches the stratosphere is expected to be photolyzed by the shorter wavelength ultraviolet light present at these altitudes to produce chlorine radicals (EPA 1979; Spence and Hanst 1978). These chlorine radicals can destroy ozone

molecules found in the stratosphere. However, since <1% of tropospheric 1,1,2,2-tetrachloroethane is expected to reach the stratosphere, release of this chemical into the atmosphere is not expected to contribute significantly to the depletion of the ozone layer (EPA 1979; WHO 1998).

6.3.2.2 Water

1,1,2,2-Tetrachloroethane undergoes base-catalyzed hydrolysis in water at environmental pH to form trichloroethylene (Cervini-Silva 2003; Cooper et al. 1987; Haag and Mill 1988). Investigators have measured the hydrolysis rate over a range of pHs. A second-order hydrolysis half-life of 102 days at 25 °C and pH 7.0 has been reported (Cooper et al. 1987). In solutions of a much lower ionic strength more typical of groundwater, empirical half-disappearance times of 573 days at pH 6.05 and 36 days at pH 7.01 were obtained for 1,1,2,2-tetrachloroethane (Haag and Mill 1988). Similarly, researchers at Dow Chemical Company found that at ppm concentrations, 1,1,2,2-tetrachloroethane undergoes abiotic transformation to trichloroethylene in a sterile, anaerobic solution at pH 7.0 (Klečka and Gonsior 1983). After 28 days, 25% of the chemical had degraded. Hydrolysis of 1,1,2,2-tetrachloroethane was not affected by contact with the low-carbon aquifer materials associated with groundwater. 1,1,2,2-Tetrachloroethane in pore-water extracted from sediments showed a 29.1-day half-life at pH values between 7.0 and 7.5 (Haag and Mill 1988). In an anoxic sediment-water system (pH unreported) the half-life of 1,1,2,2-tetrachloroethane was 6.6 days (Jafvert and Wolfe 1987). Chemical hydrolysis and biodegradation were competing processes. 1,1,2,2-Tetrachloroethane (8.4 mg/L) was degraded by 100% after 4 days in anaerobic cell free extract with a reducing agent included and by approximately 35% after 13 days in this extract without a reducing agent (Chen et al. 1996).

Lorah and Olsen (1999a, 1999b) reported that 1,1,2,2-tetrachloroethane (300 µg/L) in groundwater from a contaminated aquifer was anaerobically degraded to levels below detection within a 1.0 m vertical distance in the upward discharge through wetland sediment under increasingly reducing conditions. 1,1,2,2-Tetrachloroethane (approximately 200 µg/L) was completely degraded 16 days after it was added to a wetland sediment and groundwater microcosm under methanogenic conditions. In contrast, only 60% of 1,1,2,2-tetrachloroethane added to a sterile microcosm was degraded after 34 days, which indicates that both biotic and abiotic processes contributed to the degradation of this substance in these microcosms. The metabolites trichloroethylene, 1,2-dichloroethylene, 1,1,2-trichloroethane, 1,2-dichloroethane, and vinyl chloride were also degraded to below detectable levels within the 1.0 m vertical distance during the field study and within 34 days after addition of 1,1,2,2-tetrachloroethane during the microcosm tests (Lorah and Olsen 1999a, 1999b; Lorah and Voytek 2004). Further environmental fate and transport

information for these degradation products can be found in their separate ATSDR profiles, which are available through the internet (http://www.atsdr.cdc.gov/toxpro2.html). The anaerobic biodegradation of 1,1,2,2-tetrachloroethane can proceed through hydrogenolysis, dichloroelimination, or dehydrochlorination (Chen et al. 1996; Ferguson and Pietari 2000; Lorah and Olsen 1999b). Probable anaerobic degradation pathways for 1,1,2,2-tetrachloroethane are shown in Figure 6-2.

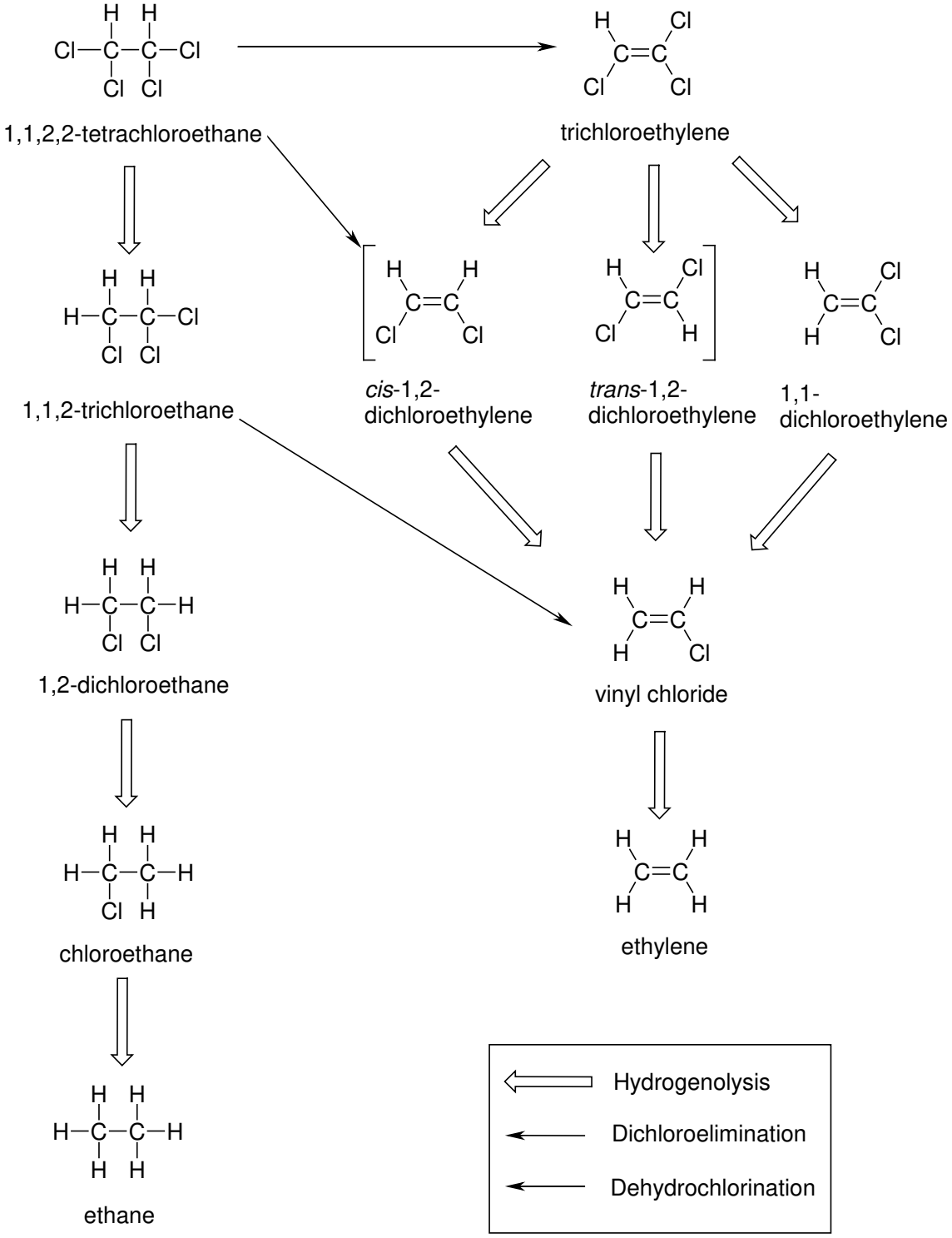
Results of aerobic biodegradability tests are conflicting. One study, in which 5 and 10 ppm of the chemical were incubated with sewage seed for 7 days, followed by 3 successive 7-day subcultures, found no significant degradation under aerobic conditions (Tabak et al. 1981). Other investigators reported that 1,1,2,2-tetrachloroethane (4.4 ppm) was degraded by 41% after 24 days in an unacclimated biodegradability test while no degradation of this substance (0.85 ppm) occurred after 5 days in a test using an acclimated seed (Mudder and Musterman 1982). A 19% loss of 1,1,2,2-tetrachloroethane (initial concentration 17.3 ppm) was obtained in a 5-day river die-away test using an acclimated system. None of the other chlorinated ethanes and ethenes in the study were found to be biodegradable. Many researchers, however, would attribute most losses involved with sewage treatment to air-stripping processes and not biodegradation (Kincannon et al. 1983).

6.3.2.3 Sediment and Soil

Based on limited information identified in the literature, both hydrolysis and anaerobic biodegradation appear to be significant transformation processes in soils and sediments.

In a study of the transformation of various chlorinated ethenes and ethanes under conditions simulating soil conditions of landfills, 1,1,2,2-tetrachloroethane was transformed into such products as 1,1,2-trichloroethane, trichloroethene, cis-1,2-dichloroethene, trans-1,2-dichloroethene, 1,1-dichloroethene, and vinyl chloride. Samples were incubated for six weeks under anaerobic conditions after inoculation with a microorganism culture obtained from the anaerobic digester of a municipal waste water treatment facility (Hallen et al. 1986). These transformations were attributed in large measure to the anaerobic microorganisms. In another study, the transformation of 1,1,2,2-tetrachloroethane in sterilized, sediment-extracted pore water was investigated (Haag and Mill 1988). After a 6-day period, approximately 34% of the original 1,1,2,2-tetrachloroethane had been transformed at pH 6.05 and a temperature of 25 °C; at the same temperature and a pH of 7.01, 74% of the 1,1,2,2-tetrachloroethane was converted. In this experiment, the transformation was attributed primarily to hydrolysis. There was little observed sorption of 1,1,2,2-tetrachloroethane to the sediment, a low-carbon sandy material.

Figure 6-2. Anaerobic Degradation Pathways for 1,1,2,2-Tetrachloroethane



Source: adapted from Lorah and Olsen 1999b

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to 1,1,2,2-tetrachloroethane depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of 1,1,2,2-tetrachloroethane in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on 1,1,2,2-tetrachloroethane levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable. The analytical methods available for monitoring 1,1,2,2-tetrachloroethane in a variety of environmental media are detailed in Chapter 7.

6.4.1 Air

Background levels of 1,1,2,2-tetrachloroethane measured in the troposphere have ranged from ≤0.1 to 0.4 ppt (Class and Ballschmiter 1986). Two air samples from rural areas of the United States did not contain detectable levels of the chemical (Brodzinsky and Singh 1982). In data collected in the late 1970s to early 1980s at 853 urban/suburban sites in the United States, the median sample concentration of 1,1,2,2-tetrachloroethane was 5.4 ppt, with values ranging from less than detection limits to a maximum of 4,800 ppt (Brodzinsky and Singh 1982). More information has subsequently been added to this database, bringing the sample size for 1,1,2,2-tetrachloroethane to 1,011 monitoring records (EPA 1988c). With the addition of the new data, the overall median was computationally at or below the database lower detection limit value of zero; 75% of the samples showed concentrations ≤8 ppt. 1,1,2,2-Tetrachloroethane was found infrequently in the air of New Jersey cities; it was found in 9 of 38 samples in Newark, 1 of 37 samples in Elizabeth, and 4 of 35 samples in Camden in the summer of 1981 (Harkov et al. 1983), and in 4 out of 105 samples from the same 3 cities in the winter of 1982 (Harkov et al. 1987). 1,1,2,2-Tetrachloroethane concentrations were <1 ppbV in urban air samples from 13 sites located in Louisiana, Texas, Vermont, and New Jersey collected from September, 1996 to August, 1997 (Mohamed et al. 2002). 1,1,2,2-Tetrachloroethane was detected above 0.07 μg/m^3 (9.8 ppt) in 609 out of 2,507 air samples collected from 25 sites across the state of Minnesota over a period of 8 years (1991–1998) (Pratt et al. 2000). The mean, median, and maximum concentrations were 0.06, 0.03, and 6.87 μg/m^3 (8.4, 4.2, and 962 ppt), respectively. Mean concentrations of 1,1,2,2-tetrachloroethane in major U.S. cities listed in

other reports ranged from trace levels below detection limits to 57 ppb (Harkov et al. 1981, 1983; Lioy et al. 1985; Singh et al. 1981, 1982; Spicer et al. 1996).

The only data on indoor levels of 1,1,2,2-tetrachloroethane were contained in a study of eight homes in Knoxville, Tennessee, obtained during the winter (Gupta et al. 1984). Ten of 16 samples (detection limits were not reported) contained 1,1,2,2-tetrachloroethane, with a mean concentration of 13.0 μg/m^3 (1.8 ppb). Although the source of the chemical was not investigated, the contamination might be attributed to consumer products used in the home or to outgassing of the chemical from construction material or household furnishings.

An EPA study of the indoor-air pollution potential associated with 1,159 common household products (Sack et al. 1992) included 1,1,2,2-tetrachloroethane as one of 31 volatile organic compounds selected for analysis. 1,1,2,2-Tetrachloroethane was found in 216 of these products. It was especially common, in trace amounts, in adhesives, oils, greases, and lubricants. Concentrations in the products were uniformly near detection limits (detection limits not reported). Although trace amounts were present in a wide variety of products, Sack et al. (1992) concluded that 1,1,2,2-tetrachloroethane has a low potential to pose unacceptable human exposure risks in indoor air.

The ranges of mean and maximum air concentrations of 1,1,2,2-tetrachloroethane in air at five NPL hazardous waste sites in New Jersey were 0.01–0.59 and 0.17–11.38 ppb, respectively, while the corresponding values for an urban landfill receiving municipal waste and nonhazardous industrial waste were 0.01 and 0.19 ppb (LaRegina et al. 1986). Samples of air surrounding the Kin-Buc waste disposal site near Edison, New Jersey contained up to 2.1 ppb of 1,1,2,2-tetrachloroethane. Air concentrations of 0.226 ppb of 1,1,2,2-tetrachloroethane were found in Iberville Parish, Louisiana along the Mississippi River, where many organic chemical production and storage facilities are located (Pellizzari 1982).

1,1,2,2-Tetrachloroethane was detected in air samples collected over the western Pacific Ocean between 43 and 4 °N; however, concentrations were not specified (Quack and Suess 1999).

6.4.2 Water

Representative samples of surface water from New Jersey were analyzed during 1977–1979 (Page 1981). These samples were collected from urban, suburban, and rural areas showing every type of land use common in the state. Sixty-seven of the 608 surface water samples (11%) contained 1,1,2,2-tetrachloro-

ethane in concentrations as high as 3.0 ppb. Concentrations of 1,1,2,2-tetrachloroethane in U.S. surface waters reported in several studies range up to 9 ppb (EPA 1977, 1980; Konasewich et al. 1978; Ohio River Valley Sanitation Commission 1980; Page 1981). According to 1999–2006 nationwide U.S monitoring data from the STORET database, 1,1,2,2-tetrachloroethane was detected in 5,343 out of 12,476 water samples (includes surface water and groundwater); however, only 391 of these detections were above the quantitation limit (unspecified). The mean, median, and range of quantifiable concentrations were 0.6, 0.5, and 0.1–25 µg/L (ppb), respectively (EPA 2006f).

Representative samples of groundwater from New Jersey were also analyzed during 1977–1979 in a project summarized in Page (1981). Sixty-four of the 1,072 groundwater samples (6%) contained 1,1,2,2-tetrachloroethane, with concentrations as high as 2.7 ppb. An example of groundwater pollution by an industrial source is the case of an abandoned organic chemical manufacturing facility in Salem, Ohio that operated from 1961 to 1973 (Khourey et al. 1984). Maximum concentrations of 1,1,2,2-tetrachloroethane were 0.501–43.0 ppm in five on-site monitoring wells and 0.556 ppm in an off-site private well. 1,1,2,2-Tetrachloroethane was detected in 5 out of 15 groundwater wells located at a landfill in Niagara Falls, New York that was contaminated with chlorinated solvents (Lee et al. 1995). 1,1,2,2-Tetrachloroethane concentrations in these wells were 1.3, 250, 14, 1.6, and 1.1 ppm. The concentration of 1,1,2,2-tetrachloroethane during 4 bimonthly analyses of a surficial aquifer at Beach Point which is located in the Edgewood Area of the U.S. Army Garrison, Aberdeen Proving Ground, Maryland ranged from 9,000 to 17,000 µg/L (ppb) (Burton et al. 2002). The water from the aquifer discharges into the Bush River, a tributary of the Chesapeake Bay. The concentration of 1,1,2,2-tetrachloroethane were below the detection limit of 0.09 µg/L (ppb) in 30 randomly distributed monitoring wells located in Wichita, Kansas during the High Plains Regional Ground-Water Study conducted in 2000 as part of the U.S. Geological Survey's National Water Quality Assessment Program (USGS 2002). The concentration of 1,1,2,2-tetrachloroethane was below 0.13 µg/L (ppb) in 34 wells (including 5 public use wells) in Cook Inlet Basin, Alaska sampled during 1999 (USGS 2001).

In the only study of rainwater located in the literature, 1,1,2,2-tetrachloroethane was not found in nine rain events in Portland, Oregon, during the spring and fall of 1982 (Pankow et al. 1984).

There is limited information on the occurrence of 1,1,2,2-tetrachloroethane in ambient surface water or groundwater used as drinking water supplies for community water supply systems. A study of 30 Canadian public water treatment facilities did not show levels of 1,1,2,2-tetrachloroethane above a 1 ppb detection limit (Otson et al. 1982). In a United States Groundwater Supply survey, none of the

945 water supplies derived from tested groundwater sources contained 1,1,2,2-tetrachloroethane at the sensitivity limit of 0.5 ppb (Westrick et al. 1984). It was detected in 1 of 13 drinking water wells in Tacoma, Washington (Shilling 1985). It was not found in any of the 1,174 community wells and 617 private wells in a Wisconsin survey conducted in the early 1980s (Krill and Sonzogni 1986). According to Round 2 data (1993–1997) reported under the EPA Unregulated Contaminant Monitoring Program (UCM), 1,1,2,2-tetrachloroethane was detected in 81 out of 166,599 samples collected from public water systems across the United States with a mean concentration of 5.0 ppb and a range of 0.05–200.00 ppb (EPA 2001b).

6.4.3 Sediment and Soil

Limited information was located on general background levels of 1,1,2,2-tetrachloroethane in soils and sediments, with most studies focusing on problems associated with the remediation of waste sites. In an analysis of test wells around RCRA disposal sites, 1,1,2,2-tetrachloroethane was documented at levels above detection limits at 25 of 479 sites from a national sample (Plumb 1991). At one waste disposal site in Pennsylvania (Sabel and Clark 1984), the concentration of 1,1,2,2-tetrachloroethane in a soil sample was 2.4 ppm. Reported concentrations of 1,1,2,2-tetrachloroethane in sediment collected from the Calcasieu River estuary in Louisiana ranged from 0 to 13.0 mg/kg (Redmond et al. 1996). According to 1999–2006 nationwide U.S. monitoring data from the STORET database, 1,1,2,2-tetrachloroethane was detected in 6 out of 635 soil samples. The mean, median, and range of 1,1,2,2-tetrachloroethane concentrations in the six samples were 0.06, 0.02, and 0.0012–0.21 mg/kg, respectively (EPA 2006f). According to STORET data, 1,1,2,2-tetrachloroethane was detected in 142 out of 335 sediment samples; however, only 3 of these detections were above the quantitation limit (unspecified). Concentrations in the three samples were 160, 130, and 180 µg/kg.

6.4.4 Other Environmental Media

The data on 1,1,2,2-tetrachloroethane in fish or other biotic tissue samples are very limited. Examination of EPA's Fish Consumption Advisory Database (EPA 1995) showed an advisory in effect for all species of fish on the lower Ashtabula River. Such fish consumption advisories are issued by states if there is some concern over the management of risks from the public eating fish caught in rivers and other water bodies. While the pollution issues in the Ashtabula River have led to cautionary warnings in the consumption of locally caught fishes, available information on bioconcentration factors summarized in

Section 6.3.1 above does not suggest a tendency for 1,1,2,2-tetrachloroethane to bioconcentrate, biomagnify, or bioaccumulate in the tissues of fish or shellfish.

1,1,2,2-Tetrachloroethane was analyzed for but not detected in approximately 90 foods during the U.S. Food and Drug Administration's Total Diet Study (TDS) (FDA 2005b). During a study of organic compounds in tobacco smoke, the concentrations of 1,1,2,2-tetrachloroethane in ultra low tar, full flavor low tar, and full flavor cigarette brands were 6.00, 3.78, and 3.19 μg/cigarette, respectively (Bi et al. 2005).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Exposure of the general population to 1,1,2,2-tetrachloroethane is expected to be very low based on the low concentrations reported for this substance in environmental media and the fact that it is no longer used as an end product. Individuals located near hazardous waste sites and facilities where this substance is used as a chemical intermediate may be exposed to 1,1,2,2-tetrachloroethane via inhalation of contaminated air, ingestion of contaminated drinking water, or dermal contact with contaminated soil. Exposures are also possible in areas around incinerators or cement kilns. Modeling estimates were made of 1,1,2,2-tetrachloroethane exposure due to inhalation and ingestion of contamination produced by incinerating chlorinated solvent waste at incinerator facilities at sites in southern California, the central Midwest, and the northern Midwest (Travis et al. 1986). For the California site, the average individual inhalation and ingestion intake was 774 and 285 μg/year, respectively. While food intake accounted for 27% of the total individual dose at the California site, this contribution was 60 and 65% for the two Midwestern sites.

A National Occupational Exposure Survey (NOES) conducted by NIOSH from 1981 to 1983 estimated that 4,145 workers are potentially exposed to 1,1,2,2-tetrachloroethane in the United States (NIOSH 2006). Of these estimated exposures, 3,666 were in occupations involving work in chemical research and development laboratories with the other exposures involving jobs in industrial chemical plants. The estimate is provisional since all the data for trade name products which may contain 1,1,2,2-tetrachloro-ethane have not been analyzed. The NOES study was based on field surveys of 4,490 facilities and was designed as a nationwide survey based on a statistical sample of virtually all workplace environments in the United States where 8 or more persons are employed (based on all Standard Industrial Classification (SIC) code workplace types except mining and agriculture) (Sieber et al. 1991). The NOES database does

not contain information on the frequency, concentration, or duration of exposure; the survey provides only estimates of workers potentially exposed to chemicals in the workplace.

According to OSHA (1991), the current 8-hour TWA permissible exposure level for 1,1,2,2-tetrachloroethane is 1 ppm. According to NIOSH (1992), the recommended exposure level for a 10-hour TWA is 1 ppm (7 mg/m^3) 1,1,2,2-tetrachloroethane.

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in Section 3.7, Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

Data regarding the exposure of children to 1,1,2,2-tetrachloroethane (including body burden data, detection in breast milk, dietary exposure data, pathways of exposure, differences in intake compared to adults, and secondary exposure data) are not available in the literature. However, based on human breast milk/blood partition coefficients of 2.26-3.55 calculated for other chlorinated alkanes (Fisher et al. 1997), it is assumed that 1,1,2,2-tetrachloroethane would readily partition to breast milk. Children who live near areas where 1,1,2,2-tetrachloroethane is released may be exposed by breathing contaminated air, by touching or eating contaminated soil, or by contact with or drinking contaminated water.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Exposures are possible for individuals living near waste disposal facilities where 1,1,2,2-tetrachloroethane site contamination has occurred. Higher exposures may occur for workers at facilities where

1,1,2,2-tetrachloroethane is still used as a chemical intermediate. Other populations with higher exposures would include people living close to NPL or other waste sites where leachates or runoff from contaminated soils could affect groundwater used for drinking water. In at least one instance, pollution from a large NPL site in Ohio has resulted in a fish consumption advisory for local recreational and subsistence fishers. Higher concentrations of 1,1,2,2-tetrachloroethane have been found in groundwater at a few locations in the United States. Individuals who use or drink the groundwater from these locations may have higher exposures to 1,1,2,2-tetrachloroethane.

6.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 1,1,2,2-tetrachloroethane is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 1,1,2,2-tetrachloroethane.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of 1,1,2,2-tetrachloroethane are well characterized and allow prediction of the environmental fate of the compound (see Table 4-2). No additional studies are required at this time.

Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The TRI, which contains this

information for 2004, became available in May of 2006. This database is updated yearly and should provide a list of industrial production facilities and emissions.

Production methods and uses for 1,1,2,2-tetrachloroethane are documented (Archer 1979; IARC 1979), but there is no recent detailed breakdown of the percentage of production consumed by each use category. Figures on current exports are also lacking. Approximately 440 million pounds (199 million kg) of 1,1,2,2-tetrachloroethane were produced in the United States in 1967 (Konietzko 1984). Production declined markedly thereafter, falling to an estimated 34 million pounds (15 million kg) by 1974. While 1,1,2,2-tetrachloroethane is apparently no longer produced as a final product, it may occur as a chemical intermediate or waste product in the manufacture of other chemicals (CEPA 1993). Better quantitative measures of current production, including production for export, is a data need for estimating the potential for environmental releases from various industries, as well as potential concentrations in the environment. Knowledge of which consumer products contain 1,1,2,2-tetrachloroethane is also a data need for estimating general population exposure. Unfortunately, this type of detailed information is difficult to obtain since companies consider it to be confidential information. While monitoring information on discharges was gathered during the 1970s and early 1980s when the EPA was developing criteria and effluent guidelines for a number of priority pollutant toxics (Shackelford et al. 1983), the TRI now constitutes the only major broad-based survey of releases to the environment. According to the most recent TRI information (TRI04 2006), releases to the air and water still continue from processing facilities in the United States. At present, the TRI data only cover major industrial sectors, so some releases may go unreported. Possible expansions of the types of facilities required to submit information under the TRI reporting requirements could help make this source of information more comprehensive.

While regulatory coverage for halogenated organic wastes has become increasingly more well defined (EPA 1989), record keeping under RCRA procedures works best when a chemical is a major constituent in a waste. Since 1,1,2,2-tetrachloroethane is now usually a minor component in other waste materials, there is often little documentation of the amounts of 1,1,2,2-tetrachloroethane entering waste disposal sites.

Environmental Fate. Half-lives and degradation rates for the atmospheric photooxidation, aqueous hydrolysis, and biodegradation of 1,1,2,2-tetrachloroethane are available. 1,1,2,2-Tetrachloroethane is quite volatile, but the highest potential for persistent pollution is when the chemical has been introduced into sediments and groundwater (Atkinson 1987; HSDB 1996; Mackay and Shiu 1981). While the chemical can be biodegraded under anaerobic conditions (Bouwer and McCarty 1983), there are major

differences under aerobic conditions (Tabak et al. 1981). Further investigation would be helpful to resolve the discrepancies in the aerobic degradation data for 1,1,2,2-tetrachloroethane and would rank as a major data need.

Bioavailability from Environmental Media. Based on available animal studies (Mitoma et al. 1985; Morgan et al. 1970; Yllner 1971) and inferences from studies of similar low molecular weight chlorinated alkanes in humans, inhalation, ingestion, and dermal exposure are the major routes of exposure (Pellizzari et al. 1982). 1,1,2,2-Tetrachloroethane in air and/or water can be expected to be absorbed readily into the systemic circulation, and 1,1,2,2-tetrachloroethane in soil may be absorbed to some extent through the skin. Analyses of 1,1,2,2-tetrachloroethane and its stable metabolites in body fluids and tissues of people exposed to the chemical is a data need to improve the knowledge base on the bioavailability of 1,1,2,2-tetrachloroethane.

Food Chain Bioaccumulation. Given its tendency to either volatilize to the atmosphere (Atkinson 1987; Mackay and Shiu 1981) or become transformed into such other chemicals as TCE (Cooper et al. 1987; Haag and Mill 1988), 1,1,2,2-tetrachloroethane shows little potential for bioaccumulation. Based on measured bioconcentration factors (ASTER 1995; Barrows et al. 1980), 1,1,2,2-tetrachloroethane is not expected to bioconcentrate and is not considered to show significant potential to bioaccumulate in food chains. No major data needs are apparent for this information category.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of 1,1,2,2-tetrachloroethane in contaminated media at hazardous waste sites are needed so that the information obtained on levels of 1,1,2,2-tetrachloroethane in the environment can be used in combination with the known body burden of 1,1,2,2-tetrachloroethane to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

In studies based on monitoring data from the late 1970s and early 1980s, 1,1,2,2-tetrachloroethane concentrations in receiving waters (primarily rivers) of at least 10 ppb were documented in approximately 10% of the samples collected in a national study of runoff from urban areas, with a maximum reported concentration of 1,400 ppb (Cole et al. 1984). In soils and sediments, information from NPL sites shows detections at 112 and 22 of 1,699 sites, respectively. Since the treatment, storage, and distribution processes used in large community drinking water systems will generally release volatile chemicals to the air, 1,1,2,2-tetrachloroethane concentrations in public drinking water are generally very low. The chemical has been detected in untreated groundwater formations used for private wells in some parts of

New Jersey (Page 1981). The highest levels have been found in groundwater in the vicinity of waste disposal sites (Khourey et al. 1984). Background levels of 1,1,2,2-tetrachloroethane in the air are typically <0.4 ppt (Brodzinsky and Singh 1982; Class and Ballschmiter 1986). Limited data collected in the vicinity of waste disposal sites has shown ambient air levels considerably higher (from >1 ppb to as high as 2.1 ppb) (Gupta et al. 1984; LaRegina et al. 1986).

Although commercial use of this substance appears to have ceased, it is still produced and used in large amounts as a chemical intermediate; therefore, the potential exists for this substance to be released in large amounts into the environment. More recent data concerning the levels of this chemical in the atmosphere as well as in soils, sediment, groundwater, and surface water are needed for determining current background concentrations and exposure levels. Reliable monitoring data for the levels of 1,1,2,2-tetrachloroethane in contaminated media at hazardous waste sites are needed, so that the information obtained on levels of 1,1,2,2-tetrachloroethane in the environment can be used in combination with the known body burdens of 1,1,2,2-tetrachloroethane to assess bioavailability and potential risks of adverse health effects in populations living in the vicinity of hazardous waste sites. Monitoring of 1,1,2,2-tetrachloroethane levels in the air of homes and buildings located near areas where this substance is released would be helpful. Although 1,1,2,2-tetrachloroethane does not appear to be present in food, additional information would be helpful in verifying this. Monitoring data on the concentrations of this substance in plants and animals in the environment are needed.

Exposure Levels in Humans. Information on exposure levels in humans is extremely limited, with most conclusions on health effects being based on inferences from animal studies (Yllner 1971). General population and occupations exposure levels have been based on models (Travis et al. 1986) or provisional estimation techniques (NIOSH 2006). Improved information on human exposure levels is therefore a data need. Information on known populations with unusually high exposures to 1,1,2,2-tetrachloroethane would be helpful.

This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Data regarding the exposure of children to 1,1,2,2-tetrachloroethane (including body burden data, detection in breast milk, dietary exposure data, pathways of exposure, differences in intake compared to adults, and secondary exposure data) are not available and would be helpful in satisfying this data need. In addition, means of decreasing exposure of children to this substance should be identified.

Child health data needs relating to susceptibility are discussed in Section 3.12.2, Identification of Data Needs: Children's Susceptibility.

Exposure Registries. No exposure registries for 1,1,2,2-tetrachloroethane were located. This substance is not currently one of the compounds for which a sub-registry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for sub-registries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

6.8.2 Ongoing Studies

No information was found to indicate that there are studies in progress that relate to the environmental fate of 1,1,2,2-tetrachloroethane (FEDRIP 2006). Similarly, no ongoing monitoring or exposure studies were identified.

7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring 1,1,2,2-tetrachloroethane, its metabolites, and other biomarkers of exposure and effect to 1,1,2,2-tetrachloroethane. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

7.1 BIOLOGICAL MATERIALS

A few studies were found in the literature that report the determination of this compound in biological matrices. The discussion about the method that may be most sensitive for the determination of tetrachloroethane levels in environmental samples and the advantages and disadvantages of the commonly used methods (see Section 7.2) are also applicable to biological samples. Because of its higher boiling point and the possibility of its loss through chemical reactions (Yasuda and Loughran 1977), the recovery of this compound from complex biological samples by most analytical methods is expected to be lower than the recoveries from air and water samples. The analytical methods for the determination of 1,1,2,2-tetrachloroethane in biological matrices are given in Table 7-1. Information about methods for metabolites of 1,1,2,2-tetrachloroethane in animal samples is given in Section 7.3.1; these methods should be applicable to human samples.

Chen et al. (1993) have reported a method for 1,1,2,2-tetrachloroethane in blood and several types of tissue from rats. Samples were homogenized with saline and isooctane, and an aliquot of the isooctane was transferred to a sampling vial for headspace/gas chromatography (GC) analysis. Fairly low detection limits (400 ng/g) and good recoveries (90–100%) were reported. Another method for volatile compounds in blood, urine, and tissues that should be applicable to the analysis of 1,1,2,2-tetrachloroethane was reported by Streete et al. (1992). In this case, headspace analysis was used to determine 1,1,2,2-tetrachloroethane in blood, urine, and tissue (after treatment with a proteolytic enzyme). The authors stress

Table 7-1. Analytical Methods for Determining 1,1,2,2-Tetrachloroethane in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Exhaled air	Collection of exhaled air through valved, Teflon spirometer in Tedlar bag; organics adsorbed onto Tenax as air is pulled through adsorbent; thermal desorption of Tenax	Cryofocus-sing HRGC/MS	No data	No data	Hartwell et al. 1987
Whole blood	Analyte adsorbed onto Tenax during purge and trap; thermal desorption onto GC column	GC/MS	500 ppt (500 ng/L)	22–27 at 1 ppb	Cramer et al. 1988
Blood	Purge and trap of 10 mL blood that was collected into specially prepared vacutainers; quantitation based on isotopically-labeled internal standards	GC/HRMS	0.005 ppb (5 ng/L)	116 at 0.063 ppb to 76 at 0.41 ppb	Ashley et al. 1992
Liver, brain, kidney, fat, heart, lung, muscle, blood	Placement of tissue into chilled 20 mL glass vials containing 2 mL ice-cold saline and 8 mL isooctane; homogenization (3–20 s depending on tissue), vortexing and centrifugation; transferring 20 µL of isooctane to 8 mL headspace vial, equilibration for 10 minutes/100 °C and injection of aliquot of headspace into GC	GC/ECD	400 ng/g (400 ppb) assuming 1 g of tissue	90–100 (average % RSD=1.7%) depending on tissue	Chen et al. 1993
Blood, urine, tissues, consumer products	Blood/urine: Equilibration of sample with internal standard in 7 mL vial at 65 °C for 15 minutes. Injection of 0.1–0.3 mL of headspace into GC using gas tight syringe	GC then split to both FID and ECD	No data	No data	Streete et al. 1992
Blood, urine, tissues, consumer products	Tissue: Placement of 20–50 mg wet mass (removed while it is frozen) into 7 mL vial with internal standard and 1 mg Subtilisin A; equilibration and analysis as for blood	GC then split to both FID and ECD	No data	No data	Streete et al. 1992
Blood, urine, tissues, consumer products	Product: Analysis of headspace after placing small volume of product into vial	GC then split to both FID and ECD	No data	No data	Streete et al. 1992

Table 7-1. Analytical Methods for Determining 1,1,2,2-Tetrachloroethane in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood, urine	Blood: 400 µL placed in a 4-mL vial fitted with a septum and placed on the heater for 30 minutes at 50 °C. The septum was pierced with the SPME syringe needle and the fiber was exposed to the headspace for 10 minutes. The fiber was then thermally desorbed for 1 minute.	SPME then GC/MS	0.5 µg/L	No data	Guidotti et al. 2001
Blood, urine	Urine: 2 mL placed in a 4-mL vial with a septum and placed on the heater for 30 minutes at 50 °C. The septum was pierced with the SPME syringe needle and the fiber was exposed to the headspace for 10 minutes. The fiber was then thermally desorbed for 1 minute.	SPME then GC/MS	4 ng/L	No data	Guidotti et al. 2001

ECD = electron capture detector; FID = flame ionization detector; GC = gas chromatography; HRGC = high resolution gas chromatography; HRMS = high resolution mass spectrometry; MS = mass spectrometry; RSD = relative standard deviation; SPME = solid phase microextraction

the importance of collecting liquid samples in a container with no headspace and keeping tissue samples frozen until a 20–50 mg piece is placed into the headspace-sampling vial. The most sensitive method found is based on purge and trap isotope dilution GC in conjunction with high resolution mass spectrometry (GC/HRMS). This method from the Centers for Disease Control and Prevention laboratory in Atlanta (Ashley et al. 1992) reported a limit of detection (LOD) for 1,1,2,2-tetrachloroethane in blood of 0.005 ppb with recoveries ranging from 116% at 0.063 ppb to 76% at 0.41 ppb. Great effort was devoted to the clean-up of collection and analysis equipment to make such LODs possible. Additional information about the mass spectrometric (MS) aspects of the method was reported by Bonin et al. (1992). Guidotti et al. (2001) describes a solid-phase microextraction (SPME) method that can be used to determine 1,1,2,2-tetrachloroethane in blood and urine. In this method, a fiber made of a fused silica support coated with the appropriate phase is exposed to sample headspace. After the appropriate amount of time has passed, the fiber is removed and thermally desorbed. Separation and detection of analytes is accomplished by GC-MS.

7.2 ENVIRONMENTAL SAMPLES

Methods for the analysis of 1,1,2,2-tetrachloroethane in environmental samples are presented in Table 7-2. There are two common methods used for the concentration of 1,1,2,2-tetrachloroethane from air. One is the direct collection of organics in a cryogenically cooled trap in line with a GC; the other method is concentration of the organic via adsorption on a sorbent column followed by thermal or solvent desorption. An advantage of the direct sampling approach is that it can be very simple. The disadvantages of the cryogenic cooling approach are that the method is cumbersome and that condensation of moisture from air may block the passage of further air flow through the trap. The sorbent-based concentration methods permit very large concentration factors and, as a result, good LODs. The disadvantages of sorbent tubes are that the sorption and desorption efficiencies may not be 100% (breakthrough during collection and poor recovery during analyte desorption) and that the background impurities in the sorbent tubes might elevate the method detection limit (Cox 1983). An additional problem with sorbent tubes is that analyte can be lost if the tube is improperly stored after sample collection. For example, Atlas and Schauffler (1991) reported losses for 1,1,2,2-tetrachloroethane of 50% when the charcoal sorbent tube was stored at room temperature for 2 days before desorption and analysis. The recoveries from the same type of tubes were very good when the tubes were stored frozen for up to 30 days after sample collection. Chemical transformation of 1,1,2,2-tetrachloroethane to trichloroethylene has been reported (NIOSH 1994) on certain types of charcoal sorbents. It is also important to note that water introduced to the GC after both cryogenic and sorbent-based collection

Table 7-2. Analytical Methods for Determining 1,1,2,2-Tetrachloroethane in Environmental Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Sample pre-concentration in liquid oxygen-cooled trap	GC/ECD	<1 ppt (<6.98 ng/m^3)	85	Singh et al. 1981
Breathing zone air	Sample collection by adsorption onto Tenax followed by thermal desorption	Cryofocussing HRGC-MS	No data	80–120	Hartwell et al. 1987; Krost et al. 1982;
Air	Sample adsorption onto Tenax followed by thermal desorption	HRGC-ECD	0.1 ppt (0.698 ng/m^3) for 1 L	No data	Class and Ballschmiter 1987
Air	Preconcentration of analyte onto Tenax-GC followed by thermal desorption onto GC column (EPA Method TO1)	GC/MS	No data	No data	EPA 1984b
Air	Collection of an aliquot of the air into a SUMMA passivated canister followed by pumping an aliquot of the air through a cryogenic trap to focus volatile organics; thermal desorption onto GC column (EPA Method TO14)	GC/MS (full scan or selected ion monitoring); GC/FID/ECD/ PID	No data; depends on air aliquot size and mode of detection	No data; generally very good for non-polar volatile organics	EPA 1984c
Air	Preconcentration of analyte onto adsorbent trap containing 5 mg charcoal followed by immediate elution of traps with 30–50 µL of redistilled benzene in 3–5 aliquots	GC/ECD	Low parts per trillion in 20 L sample	85	Atlas and Schauffler 1991
Air	Passive collection onto carbon-based badge (3M OVM 3500); extraction with carbon disulphide containing internal standard	GC/MS (SIM)	<1 µg/m^3 (0.14 ppb)	89.3	Otson et al. 1994

Table 7-2. Analytical Methods for Determining 1,1,2,2-Tetrachloroethane in Environmental Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Equilibration of air with polymer-coated fiber for analyte concentration followed by thermal desorption of fiber (SPME)	GC/MS	0.06 ppbv (1.5% RSD)	70–98 depending on how fiber is stored after collection	Chai and Pawliszyn 1995
Air	Direct injection of 1 mL air into GC and cryogenic focusing (-150 °C) of volatiles followed by rapid heating to +150 °C in 20 minutes.	High speed GC/FID	2 ppb (14 µg/m^3) (depends on retention time)	No data	Mouradian et al. 1991
Occupational air	Preconcentration of analyte from air onto solid sorbent tube (petroleum charcoal); desorption with CS_2 and injection of 5 µL into GC. Working range is 1.5–15 ppm (10–100 mg/m^3) for a 10 L air sample. (NIOSH Method 1019)	GC/FID	0.01 mg/sample (0.3 mg/m^3 for 30 L sample volume)	106	NIOSH 1994
Air from waste and landfill sites	Adsorption of analyte onto Tenax followed by thermal desorption	Cryofocussing HRGC-MS or HRGC-ECD	0.01–0.1 ppb (0.07–0.7 µg/m^3)	No data	Gianti et al. 1984; LaRegina et al. 1986
Treated and raw source water	Purge and trap followed by thermal desorption	GC/MS	<1.0 µg/L	90	Otson 1987
Treated and raw source water	Purging of sample and on-column trapping	GC/FID and GC/HECD	1 µg/L (FID); 0.5 µg/L (HECD)	24 (HECD)	Otson and Williams 1982
Finished drinking/raw source water	Purge and trap onto Tenax/silica/charcoal followed by thermal desorption	Subambient programmable HRGC-MS (EPA Method 524.1)	0.28–0.41 µg/L	111 at 1 µg/L	EPA 1986c
Finished drinking/raw source water	Purge and trap onto Tenax/silica/charcoal followed by thermal desorption	Cryofocussing (wide or narrow bore) HRGC-MS (EPA Method 524.2)	0.04 µg/L (wide bore), 0.20 µg/L (narrow bore)	91 at 0.4–10 µg/L (wide bore), 100 at 0.5 µg/L (narrow bore)	EPA 1986d

Table 7-2. Analytical Methods for Determining 1,1,2,2-Tetrachloroethane in Environmental Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Finished drinking water, raw source water, or drinking water in any treatment stage	Purging of organics from water using inert gas and trapping onto a sorbent; thermal desorption onto GC (EPA Method 502.2)	GC/PID (10.0 eV nominal)/ ELCD	0.01 µg/L with ELCD (no response from PID)	99 (6.8% RSD)	EPA 1988b
Drinking water, raw source water, or drinking water in any treatment stage	Purging of organics from water using inert gas and trapping onto a sorbent; thermal desorption of compounds onto GC (EPA Method 502.1)	GC/ electrolytic conductivity or GC/micro-coulometric detector	0.01 µg/L	95 (n=18) at 0.40 µg/L	EPA 1988a
Water	Purge and trap (Standard Methods 6210D; equivalent to EPA Method 524)	GC/MS	0.02–0.2 µg/L	100 (12% RSD for n=7) at 0.5 µg/L (narrow bore capillary column)	APHA 1989a
Water	Purge and trap (Standard Methods 6230D; equivalent to EPA Method 502.2)	GC/PID/ ELCD or micro-coulometric detector	0.1–0.05 µg/L	99 at 10 µg/L; SD=6.8 µg/L	APHA 1989b
Water	Addition of isotopically labeled analogs of compounds of interest to the water sample followed by purge and trap (EPA-EAD Method 1624)	GC/MS	10 µg/L	Not available	EPA 2001
Water	Purge and trap (ASTM Method D5790)	GC/MS	0.19 µg/L	101	NEMI 2001
Water	Purge and trap (Standard Methods 6200B)	GC/MS	0.06 µg/L	104	NEMI 1997a
Water	Purge and trap (Standard Methods 6200C)	GC/ELCD	0.03 µg/L	88	NEMI 1997b
Water	Purge and trap followed by thermal desorption (USGS-NWQL Method O-3115)	GC/MS	3 µg/L	Not available	USGS 1983

Table 7-2. Analytical Methods for Determining 1,1,2,2-Tetrachloroethane in Environmental Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water	Purge and trap (USGS-NWQL Method O-4127-96)	GC/MS	0.077 µg/L	95–116.7	USGS 1998
Municipal and industrial waste water	Purging of organics from water using inert gas and trapping onto a sorbent. Thermal desorption of compounds onto GC. (EPA Method 601)	GC/ electrolytic conductivity or GC/micro-coulometric detector	30 ng/L (depending on interferences)	0.95 c+0.19 where c=true value for concentration in µg/L	EPA 1984a
Groundwater and solid wastes	Purge and trap (EPA Method 8240)	GC/MS	Groundwater: 5 µg/L; soil/ sediment: 5 µg/kg. Both values for fairly clean matrix; LODs much worse for complex wastes	0.93 c+1.76 where c is concentration in µg/L	EPA 1986a
Waste water	Purge and trap onto Tenax/silica followed by thermal desorption	GC/MS (EPA Method 624)	6.9 µg/L	102 at 10–1,000 µg/L	EPA 1982a
Groundwater and surface water	Cryogenic trapping of analyte released into reduced pressure headspace (modification of vacuum distillation)	GC/ECD	1 ng/L	48	Comba and Kaiser 1983
Groundwater	Purge and trap onto Tenax/silica followed by thermal desorption	GC/MS (EPA-CLP Method)	5 µg/L	No data	EPA 1987
Fish	Vacuum distillation and cryogenic trapping	HRGC/MS	No data	No data	Hiatt 1983

Table 7-2. Analytical Methods for Determining 1,1,2,2-Tetrachloroethane in Environmental Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Various fatty and non-fatty foods and beverages	Extraction of clear beverages with isooctane. Homogenization of composited food with >70% fat or oil and direct dilution or melting followed by dilution with isooctane. Preparation of other foods with solid or pulpy consistency via extraction with 20% acetone -5% NaCl in 25% phosphoric acid and isooctane. Isooctane analyzed directly by GC. Extracts from samples containing 21–70% fat had fat removed using Florisil.	GC/ECD or GC/ELCD	No data	Florisil treated: 38–122 (mean=80%, CV=23%); non-Florisil treated: 8–89 (mean=57%, CV=38%)	Daft 1989
Soil and sediment	Purging of sample suspension in water, adsorption of volatiled compounds onto Tenax/silica followed by thermal desorption	GC/MS	5 µg/kg	No data	EPA 1987
Sediment	Purge and trap with collection of released compounds onto Porapak followed by desorption with methanol	HRGC/ECD	1 µg/kg	60–82	Amin and Narang 1985
Sediment	Extraction of sediment with methanol followed by transfer of an aliquot of methanol extract to water for purge and trap analysis	GC/ECD/FID	0.05 µg/g (ppm)	84–86 (7% RSD)	Amaral et al. 1994
Sewage sludge	Extraction with pentane, addition of internal standard, filtration	GC/ECD	0.08 µg/L (wet)	111 (10.6% RSD)	Wilson et al. 1994

Table 7-2. Analytical Methods for Determining 1,1,2,2-Tetrachloroethane in Environmental Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Liquid and solid waste	Dispersion of solid and viscous samples in a glycol followed by purge and trap using Tenax/silica/ charcoal and thermal desorption	GC/HECD (EPA Method 5030 and 8010)	0.3 µg/L (groundwater); 0.3 µg/kg (soil); 15 µg/L (liquid waste); 37.5 µg/kg (sludge or solid waste)	0.95 c+0.19 where c is actual concentration	EPA 1982b, 1986b
Solid and liquid waste	Dispersion of solid and viscous samples in a glycol followed by purge and trap using Tenax/silica/ charcoal and thermal desorption	GC/HECD and PID in series	0.9 µg/L (water 1–5 mg/kg (soil)	93 at 6 µg/L (water)	Lopez-Avila et al. 1987
Groundwater and solid waste	Purge and trap direct injection, vacuum distillation, or head space (EPA-OSW 8021B)	GC/HECD and/or PID	0.01 µg/L (HECD); not available (PID)	99 (HECD); not available (PID)	EPA 1996b
Air, water, solid waste	Purge and trap (aqueous, solid, and waste oil), direct injection (waste oil), automatic static headspace (solid), closed system vacuum distillation (aqueous, solid, oil, and tissue), or desorption from trapping media (air) (EPA-OSW 8260B)	GC/MS	0.04 µg/L (wide-bore capillary column); 0.20 µg/L (narrow-bore capillary column)	91 (wide-bore capillary column); 100 (narrow-bore capillary column)	EPA 1996a

[a]For liquid samples: ppm = mg/L; ppb = µg/L; ppt = ng/L; for air samples: ppbv = nmoles analyte:liter air

ECD = electron capture detector; ELCD = electrolytic conductivity detector; FID = flame ionization detector; GC = gas chromatography; HECD = hall electrolytic conductivity detector; HRGC = high resolution gas chromatography; MC = microcoulometry; MS = mass spectrometry; PID = photoionization detector; RSD = relative standard deviation (coefficient of variation); SD = standard deviation; SIM = selected ion monitoring; SPME = solid phase microextraction

methods can result in shifts in GC retention times and in the alteration of instrumental response in MS detection that results from pressure changes in the ion source during elution of the water.

The most common method for the determination of 1,1,2,2-tetrachloroethane levels in water, sediment, soil, and other high solid samples is to purge the compound with an inert gas from the sample directly or after suspension of the sample in water, and to trap the purged vapors onto a sorbent trap (purge and trap). Subsequent thermal desorption is used for the determination of the analyte concentration. Different purging methods have been compared by Melton et al. (1981). Purge and trap methods for source and drinking water have also been described by Otson (1987) and Otson and Williams (1982). A purge and trap method has even been adapted and applied to highly radioactive waste samples (Tomkins et al. 1989). Dynamic thermal stripping is a variation of the purge and trap method. It has been shown to extend the range of analyte molecular weights that can be accessed using this type of methodology (Lesage 1991). The determination of 1,1,2,2-tetrachloroethane can be accomplished by both the purge and trap and dynamic thermal stripping methods. Matz and Kesners (1993) have described a "spray and trap" method in which the sample is continuously sprayed into a container that is swept with gas to transport the volatilized organics to a sorbent trap. Unlike the bubble stripping of purge and trap, the spray extraction offers a continuous analyte flux of constant concentration for optimum trapping conditions. A publication by Daft (1989) demonstrates the poor accuracy that can result when liquid/liquid extraction approaches are applied to samples containing volatile organic compounds.

Standardized methods used for detection of 1,1,2,2-tetrachloroethane in water samples by purge and trap followed by GC/MS include EPA Methods 524.2, 624, and 1624, Standard Methods 6200B and 6200C, ASTM Method D5790, and USGS-NWQL Methods O-4127-96 and O-3115 (EPA 1982a, 1986b, 2001a; NEMI 1997a, 1997b, 2001; USGS 1983, 1998). Detection limits and percent recoveries for determination of this substance in water are 0.02–10 ppb and 88–116.7%, respectively, using these methods. EPA-OSW Methods 8021B and 8260B can be applied to solid waste samples. Method 8021B uses GC followed by a photoionization detector (PID) and a Hall electron capture detector (HECD) connected in series (EPA 1996a, 1996b).

The two routine quantification methods that provide the lowest detection limits are halogen-specific detection (e.g., Hall electrolytic conductivity detector) and MS. Since the compound has four chlorine atoms, electron capture detection (ECD) is also very sensitive for this compound. The advantages of halogen-specific detectors are they are not only very sensitive, but are also selective for halogen-containing compounds. The mass spectrometer, on the other hand, provides additional confirmation of

the presence of a compound through the compound's characteristic fragmentation pattern, and this selectivity can be very desirable when the simultaneous quantification of many compounds is required. The inability of halogen-specific detectors to detect and quantify nonhalogen compounds can be overcome by using other detectors (e.g., photoionization detector) in series (Driscoll et al. 1987; Lopez-Avila et al. 1987). Atomic emission detectors can provide signals from many elements within the molecule (C, H, and Cl for 1,1,2,2-tetrachloroethane) simultaneously (Ryan et al. 1990; Yieru et al. 1990a, 1990b). A detection limit of 10 pg 1,1,2,2-tetrachloroethane was reported using a helium discharge detector in conjunction with GC (Ryan et al. 1990).

High-resolution gas chromatography (HRGC) with capillary columns is a better method for volatile compounds than packed columns because capillary columns provide better resolution of closely eluting compounds and increase the sensitivity of detection. Sample purge and on-column cryotrapping can eliminate the need for the conventional purge and trap unit and can reduce the time of analysis (Pankow and Rosen 1988). Although this approach is most easily accomplished using packed columns, capillary columns can provide better separation and method sensitivity. The plugging of the trap (or column) by moisture condensation during cryotrapping in an open tubular column can be avoided through the use of a very wide bore capillary column; the chromatographic resolution of such a column is inferior to narrow bore capillary columns (Mosesman et al. 1987; Pankow and Rosen 1988) and limits the method sensitivity.

7.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 1,1,2,2-tetrachloroethane is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 1,1,2,2-tetrachloroethane.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. A few methods were found for the determination of 1,1,2,2-tetrachloroethane levels of biological matrices. The most sensitive method found was that of Ashley et al. (1992) in which the LOD for 1,1,2,2-tetrachloroethane in human blood was reported to be 0.005 ppb with a recovery of 116% at 0.063 ppb. Chen et al. (1993) reported methods for the determination of this compound in blood and tissues from rats that were used to study the toxicokinetics of 1,1,2,2-tetrachloroethane after intra-arterial administration. The LOD reported was 400 ng/g, depending on the tissue, with 90–100% recovery and an average precision of 1.7% relative standard deviation (RSD). The methods for rat tissues should be applicable to human tissues, but have not been evaluated. The study of the levels of the parent compound in human blood, urine, or other biological matrices can be useful in deriving a correlation between levels of this compound in the environment and those in human tissue or body fluid. Such controlled correlation studies are unavailable for this compound.

No metabolite or biomarker of 1,1,2,2-tetrachloroethane from human exposure specific to this compound has yet been identified (see Section 3.8). The changes in metabolite concentrations with time in human blood, urine, or other appropriate biological medium may be useful in estimating its rate of metabolism in humans. In some instances, a metabolite or a biomarker might be useful in correlating the exposure doses to the human body burden but, as previously noted, the metabolites are not specific to 1,1,2,2-tetrachloroethane. Such studies on the levels of metabolites/biomarkers in human samples are not available for this compound, although metabolic products of this compound from animal and *in vitro* studies have been identified (see Chapter 3) and analytical methods for their quantification are available. The metabolites, chloral hydrate, trichloroethanol, trichlorethanol glucuronide, and trichloroacetic acid, have all been determined using variations of headspace analysis (Breimer et al. 1974; Christensen et al. 1988; Koppen et al. 1988). These compounds are metabolites of TCE that can be formed from 1,1,2,2-tetrachloroethane. Reported sensitivities were approximately 20 ng/mL (20 ppb). Assuming a greater abundance in urine of metabolites relative to parent compound, these methods might be adequate but this has not been demonstrated. Additional methods need to be validated or developed to detect metabolites of 1,1,2,2-tetrachloroethane after exposures at the MRLs.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. The occurrence of this compound in environmental media can be used to indicate possible

exposure of humans to this compound through the inhalation of air and ingestion of drinking water and foods containing 1,1,2,2-tetrachloroethane. The MRL for intermediate-duration inhalation exposure is 0.4 ppm (see Section 2.3). Methods for the measurement of 1,1,2,2-tetrachloroethane in air at the ppt level and at least 85% accuracy are available (Atlas and Schauffler 1991; Class and Ballschmiter 1987; Singh et al. 1981). No new methods are needed for this compound in air. Methods for the measurement of 1,1,2,2-tetrachloroethane in drinking water are sensitive to sub-ppb (sub-µg/L) and ppt (ng/L) levels with 91–100% accuracy (APHA 1989a, 1989b; EPA 1986c, 1988b). No new methods are needed for drinking water. Very little information was found for 1,1,2,2-tetrachloroethane in food; additional detection methods are needed for foods.

Although the products of biotic and abiotic processes of this compound in the environment are adequately known, no systematic study is available that measures the concentrations of its reaction products in the environment. In instances where the product(s) of an environmental reaction is more toxic than the parent compound, it is important to know the level of the reaction products in the environment. It is known that 1,1,2,2-tetrachloroethane degrades under anaerobic conditions (e.g., in anaerobic landfills, leading to contamination of groundwater) and via hydrolysis to trichloroethylene (see Section 6.3.2, and Cooper et al. [1987] and Haag and Mill [1988]). Hallen et al. (1986) also reported isolating 1,1,2-trichloroethane, cis-1,2-dichloroethylene, trans-1,2-dichloroethylene, 1,1-dichloroethylene, and vinyl chloride after 6 weeks of incubation of 1,1,2,2-tetrachloroethane in a simulated landfill. The analytical methods for the determination of the levels of these environmental reaction products of 1,1,2,2-tetrachloroethane are available. Drinking water would be expected to be the main route of oral exposure. All of these compounds can be measured in drinking water using EPA Method 502.2 (EPA 1988b). Method detection limits (µg/L) are stated to be 0.01 for trichloroethylene, not determined for 1,1,2-trichloroethane, 0.01 for cis-1,2-dichloroethylene, 0.05 for trans-1,2-dichloroethylene, 0.07 for 1,1-dichloroethylene, and 0.02 for vinyl chloride. Precisions were reported to be between 2 and 4% RSD. All of the stated degradation products except cis- and trans-1,2-dichloroethylene can be measured in soils and solid wastes using EPA method 8240 (EPA 1986a) with practical quantitation limits (PQLs) of approximately 5 µg/L in groundwater, 5 µg/kg in soils/sediments, and 0.5 mg/kg in wastes. All of the degradation products except cis-1,2-dichloroethylene can be measured in municipal and industrial wastes with PQLs ranging from 0.02 µg/L for 1,1,2-trichloroethane to 0.18 µg/L for vinyl chloride. Assuming that the concentrations of these degradation products are much less than the concentration of 1,1,2,2-tetrachloroethane and knowing that the methods for the parent compound are sufficiently sensitive to measure background levels, no additional methods are needed at the present time.

7.3.2 Ongoing Studies

The Environmental Health Laboratory Sciences Division of the National Center for Environmental Health, Centers for Disease Control and Prevention, is developing methods for the analysis of 1,1,2,2-tetrachloroethane and other volatile organic compounds in blood. These methods use purge and trap methodology, HRGC, and magnetic sector MS, which gives detection limits in the low ppt range.

No other ongoing studies related to analytical methods were identified.

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8. REGULATIONS AND ADVISORIES

The international and national regulations and guidelines regarding 1,1,2,2-tetrachloroethane in air, water, and other media are summarized in Table 8-1.

ATSDR has derived an intermediate-duration oral MRL of 0.5 mg/kg/day for 1,1,2,2-tetrachloroethane based on a liver effect (minimal hepatocyte necrosis) in female rats administered the chemical in the diet for 14 weeks (NTP 2004a). The MRL was derived using benchmark dose modeling of the critical end point. The BMD corresponding to a BMR of 10% extra risk is 82.89 mg/kg/day; the corresponding $BMDL_{10}$ is 53.88 mg/kg/day. An uncertainty factor of 100 (10 for interspecies extrapolation and 10 for human variability) was applied to the $BMDL_{10}$ to calculate the MRL.

An EPA oral reference dose (RfD) and inhalation reference concentration (RfC) for 1,1,2,2-tetrachloroethane have not been derived.

The IARC classification for 1,1,2,2-tetrachloroethane is Group 3, not classifiable with regard to its carcinogenicity to humans (IARC 2004). The EPA cancer classification for 1,1,2,2-tetrachloroethane is Group C, possible human carcinogen (IRIS 2006). The National Toxicology Program has not classified 1,1,2,2-tetrachloroethane for human carcinogenicity (NTP 2004b). The American Conference of Governmental Industrial Hygienists (ACGIH) has classified 1,1,2,2-tetrachloroethane as an A3 carcinogen (confirmed animal carcinogen with unknown relevance to humans) (ACGIH 2005).

OSHA requires employers of workers who are occupationally exposed to 1,1,2,2-tetrachloroethane to institute engineering controls and work practices to reduce and maintain employee exposure at or below permissible exposure limits (PEL) (OSHA 2006c). The employer must use engineering and work practice controls to reduce exposure to or below an 8-hour time-weighted average (TWA) of 5 ppm (OSHA 2006c). Respirators must be provided and used during the time period necessary to install or implement feasible engineering and work practice controls (OSHA 2006c). ACGIH (2005) and NIOSH (2005) recommend a TWA exposure limit of 1 ppm for occupational exposure.

1,1,2,2-Tetrachloroethane is regulated by the Clean Water Effluent Guidelines as stated in Title 40, Section 400–475, of the Code of Federal Regulations. For each point source category, 1,1,2,2-tetrachloroethane may be regulated as one of a group of chemicals controlled as Total Toxic Organics, or may

have a Zero Discharge Limitation. The point source categories for which 1,1,2,2-tetrachloroethane is controlled as a Total Toxic Organic include electroplating, metal finishing, and coil coating; see electronic Code of Federal Regulations for a complete listing (NARA 2006).

EPA regulates 1,1,2,2-tetrachloroethane under the Clean Air Act (CAA) and has designated it as a hazardous air pollutant (HAP) (EPA 2006a). 1,1,2,2-Tetrachloroethane is on the list of chemicals appearing in "The Emergency Planning and Community Right-to-Know Act of 1986" (EPCRA) (EPA 2006c) and has been assigned a reportable quantity (RQ) limit of 100 pounds (EPA 2006b). The RQ represents the amount of a designated hazardous substance which, when released to the environment, must be reported to the appropriate authority.

Table 8-1. Regulations and Guidelines Applicable to 1,1,2,2-Tetrachloroethane

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	Group 3[a]	IARC 2004
WHO	Air quality guidelines	No data	WHO 2000
	Drinking water quality guidelines	No data	WHO 2004
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)	1 ppm[b]	ACGIH 2005
EPA	AEGL	No data	EPA 2006h
	Hazardous air pollutant	Yes	EPA 2006a 42 USC 7412
NIOSH	REL (10-hour TWA)	1 ppm[c,d]	NIOSH 2005
	IDLH	100 ppm[c]	
OSHA	PEL (8-hour TWA) for general industry	5 ppm[e]	OSHA 2006c 29 CFR 1910.1000
	PEL (8-hour TWA) for construction industry	5 ppm[e]	OSHA 2006b 29 CFR 1926.55, Appendix A
	PEL (8-hour TWA) for shipyard industry	5 ppm[e]	OSHA 2006a 29 CFR 1915.1000
b. Water			
DOT	Marine pollutant	Yes	DOT 2005 9 CFR 172.101, Appendix B
EPA	Drinking water standards and health advisories		EPA 2006i
	1-day health advisory for a 10-kg child	0.04 mg/L	
	10-day health advisory for a 10-kg child	0.04 mg/L	
	DWEL	0.002 mg/L	
	Lifetime	$3x10^{-4}$ mg/L	
	10^{-4} Cancer risk	0.02 mg/L	
	National primary drinking water standards	No data	EPA 2003
	National recommended water quality criteria		EPA 2006j
	Human health for consumption of water + organism	0.17 μg/L	
	Human health for consumption of organism only	4.0 μg/L	
	Toxics criteria for those states not complying with Clean Water Act Section 303(c)(2)(B) for human health (10^{-6} risk for carcinogens) for consumption of:		EPA 2006g 40 CFR 131.36
	Water + organism	0.17 μg/L	
	Organism only	11 μg/L	

Table 8-1. Regulations and Guidelines Applicable to 1,1,2,2-Tetrachloroethane

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
c. Food			
FDA	Bottled drinking water	No data	FDA 2005a 21 CFR 165.110
d. Other			
ACGIH	Carcinogenicity classification	A3[f]	ACGIH 2005
EPA	Carcinogenicity classification	Group C[g]	IRIS 2006
	Oral slope factor	$2x10^{-1}$ per mg/kg/day	
	Inhalation unit risk	$5.8x10^{-5}$ per µg/m^3	
	RfC	No data	
	RfD	No data	
	Identification and listing of hazardous waste; hazardous waste number	U209	EPA 2006k 40 CFR 261, Appendix VIII
	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance	Yes	EPA 2006b 40 CFR 302.4
	Reportable quantity	100 pounds	
	Effective date of toxic chemical release reporting	01/01/87	EPA 2006c 40 CFR 372.65
NTP	Carcinogenicity classification	No data	NTP 2004b

[a]Group 3: not classifiable as to carcinogenicity to humans
[b]Skin notation: refers to the potential significant contribution to the overall exposure by the cutaneous route, including mucous membranes and the eyes, either by contact with vapors, liquids, or solids.
[c]Potential occupational carcinogen
[d]Skin designation: indicates the potential for dermal absorption; skin exposure should be prevented as necessary through the use of good work practices, gloves, coveralls, goggles, and other appropriate equipment.
[e]Skin designation
[f]A3: confirmed animal carcinogen with unknown relevance to humans
[g]Group C: possible human carcinogen

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = Acute Exposure Guideline Level; CERCLA = Comprehensive Environmetnal Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; DOT = Department of Transportation; DWEL = drinking water equivalent level; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; MCLG = maximum contaminant level goal; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; STEL = short-term expsoure limit; TLV = threshold limit values; TWA = time-weighted average; USC = United States Code; WHO = World Health Organization

9. REFERENCES

ACGIH. 2005. Threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienists.

Adinolfi M. 1985. The development of the human blood-CSF-brain barrier. Dev Med Child Neurol 27:532-537.

Adlercreutz H. 1995. Phytoestrogens: Epidemiology and a possible role in cancer protection. Environ Health Perspect Suppl 103(7):103-112.

Agency for Toxic Substances and Disease Registry. 1989. Decision guide for identifying substance-specific data needs related to toxicological profiles. Atlanta, GA: Agency for Toxic Substances and Disease Registry, Division of Toxicology. Fed Regist 54(174):37618-37634.

*Agency for Toxic Substances and Disease Registry. 1996. Toxicological profile query; list of all toxicological profiles. Atlanta, GA: Agency for Toxic Substances and Disease Registry. http://www.atsdr.cdc.gov/toxpro2.html. April 17, 2006.

Agency for Toxic Substances and Disease Registry. 1997. Toxicological profile for tetrachloroethylene (update). Atlanta, GA: Agency for Toxic Substances and Disease Registry. PB98101181AS. http://www.atsdr.cdc.gov/toxprofiles/tp18.html. July 15, 2006.

AIChE. 1995. 1,1,2,2-Tetrachloroethane. C2H2Cl4. In: Physical and thermodynamic properties of pure chemicals. American Institute of Chemical Engineers, Design Institute for Physical Property Data. Philadelphia, PA: Taylor and Francis.

Altman PL, Dittmer DS. 1974. Biological handbooks: Biology data book. Vol. III. 2nd ed. Bethesda, MD: Federation of American Societies for Experimental Biology, 1987-2008, 2041.

Amaral OC, Olivella L, Grimalt JO, et al. 1994. Combined solvent extraction-purge and trap method for the determination of volatile organic compounds in sediments. J Chromatogr 675(1-2):177-187.

Amin TA, Narang RS. 1985. Determination of volatile organics in sediment at nanogram-per-gram concentrations by gas chromatography. Anal Chem 57:648-651.

Amoore JE, Hautala E. 1983. Odor as an aid to chemical safety: Odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. J Appl Toxicol 3:272-290.

Andersen ME, Krishnan K. 1994. Relating in vitro to in vivo exposures with physiologically based tissue dosimetry and tissue response models. In: Salem H, ed. Animal test alternatives: Refinement, reduction, replacement. New York, NY: Marcel Dekker, Inc., 9-25.

Andersen ME, Clewell HJ III, Gargas ML, et al. 1987. Physiologically based pharmacokinetics and the risk assessment process for methylene chloride. Toxicol Appl Pharmacol 87:185-205.

*Not cited in text

9. REFERENCES

APHA. 1989a. Method 6210D. Purge and trap capillary column gas chromatography/mass spectrometric method. In: Standard methods for the examination of water and wastewater. 17th ed. Washington, DC: American Public Health Association, American Water Works Association, Water Pollution Control Federation.

APHA. 1989b. Method 6230D. Purge and trap capillary-column gas chromatographic method. In: Standard methods for the examination of water and wastewater. 17th ed. Washington, DC: American Public Health Association, American Water Works Association, Water Pollution Control Federation.

Archer WL. 1979. Other chloroethanes. In: Grayson H, Eckroth D, eds. Kirk-Othmer encyclopedia of chemical technology. 3rd ed. Vol. 5. New York, NY: John Wiley and Sons, 722-742.

Arthur D. Little, Inc. 1983. Cell transformation assays of 11 chlorinated hydrocarbon analogs (final report). ICAIR work assignment no. 10. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8E. OTS0509392.

Ashley DL, Bonin MA, Cardinalis FL, et al. 1992. Determining volatile organic compounds in human blood from a large sample population by using purge and trap gas chromatography/mass spectrometry. Anal Chem 64:1021-1029.

ASTER. 1995. ASTER ecotoxicity profile. Duluth, MN: Assessment Tools for the Evaluation of Risk (ASTER). U.S. Environmental Protection Agency. Environmental Research Laboratory. October 11, 1995.

Atkinson R. 1987. A structure-activity relationship for the estimation of rate constants for gas-phase reaction of OH radicals with organic compounds. Int J Chem Kinet 19:799-828.

Atlas E, Schauffler S. 1991. Analysis of alkyl nitrates and selected halocarbons in the ambient atmosphere using a charcoal preconcentration technique. Environ Sci Technol 25(1):61-67.

Barnes D, Dourson M. 1988. Reference dose (RfD): Description and use in health risk assessments. Regul Toxicol Pharmacol 8:471-486.

Barrows ME, Petrocelli SR, Macek KJ, et al. 1980. Bioconcentration and elimination of selected water pollutants by bluegill sunfish (Lepomis macrochirus). In: Haque R, ed. Dynamics, exposure, and hazard assessment of toxic chemicals. Ann Arbor, MI: Ann Arbor Science, 379-392.

Berger GS. 1994. Epidemiology of endometriosis. In: Berger GS, ed. Endometriosis: Advanced management and surgical techniques. New York, NY: Springer-Verlag, 3-7.

Bi X, Sheng G, Feng Y, et al. 2005. Gas- and particulate-phase specific tracer and toxic organic compounds in environmental tobacco smoke. Chemosphere 61(10):1512-1522.

*Bollman JL, Mann FC. 1931. Experimentally produced lesions of the liver. Ann Intern Med 5:699-712.

Bonin MA, Ashley DL, Cardinali FL, et al. 1992. Importance of enhanced mass resolution in removing interferences when measuring volatile organic compounds in human blood by using purge-and-trap gas chromatography/mass spectrometry. J Am Soc Mass Spectrom 3:831-841.

9. REFERENCES

Borisover MD, Graber ER. 1997. Specific interactions of organic compounds with soil; organic carbon. Chemosphere 34(8):1761-1776.

Bouwer EJ, McCarty PL. 1983. Transformations of 1- and 2-carbon halogenated aliphatic organic compounds under methanogenic conditions. Appl Environ Microbiol 45:1286-1294.

Breimer DD, Ketelaars HCJ, Van Rossum JM. 1974. Gas chromatographic determination of chloral hydrate, trichloroethanol and trichloroacetic acid in blood and in urine employing head-space analysis. J Chromatogr 88:55-63.

Brem H, Stein AB, Rosenkranz HS. 1974. The mutagenicity and DNA-modifying effect of haloalkanes. Cancer Res 34:2576-2579.

Brodzinsky R, Singh HB. 1982. Volatile organic chemicals in the atmosphere: An assessment of available data. Menlo Park, CA: Atmospheric Science Center, SRI International, 99-100.

Bull RJ, Sanchez IM, Nelson MA, et al. 1990. Liver tumor induction in B6C3F1 mice by dichloroacetate and trichloroacetate. Toxicology 63:341-359.

Burton DT, Dilorenzo JL, Shedd TR, et al. 2002. Aquatic hazard assessment of a contaminated surficial aquifer discharge into the Bush River, Maryland (USA). Water Air Soil Pollut 139(1-4):159-182.

Callen DF, Wolf CR, Philpot RM. 1980. Cytochrome P-450 mediated genetic activity and cytotoxicity of seven halogenated aliphatic hydrocarbons in Saccharomyces cerevisiae. Mutat Res 77:55-63.

Carpenter CP, Smyth HF, Pozzani UC. 1949. The assay of acute vapor toxicity and the grading and interpretation of results on 96 chemical compounds. J Ind Hyg Tox 31:343-346.

Casciola LAF, Ivanetich KM. 1984. Metabolism of chloroethanes by rat liver nuclear cytochrome P-450. Carcinogenesis 5:543-548.

CEPA. 1993. 1,1,2,2,-Tetrachlorethane: Priority substances list assessment report. Ottawa, Canada: Canada Environmental Protection Act, Priority Substance List Assessment Report.

Cervini-Silva J. 2003. Linear free-energy relationship analysis of the fate of chlorinated 1- and 2-carbon compounds by redox-manipulated smectite clay minerals. Environ Toxicol Chem 22(10):2298-2305.

Chai M, Pawliszyn J. 1995. Analysis of environmental air samples by solid-phase microextraction and gas chromatography/ion trap mass spectrometry. Environ Sci Technol 29(3):693-701.

Charbonneau M, Greselin E, Brodeur J, et al. 1991. Influence of acetone on the severity of the liver injury induced by haloalkane mixtures. Can J Physiol Pharmacol 69:1901-1907.

ChemID. 2004. 1,1,2,2-Tetrachloroethane. ChemIDplus. National Library of Medicine. http://chem.sis.nlm.nih.gov/chemidplus/cmplxqry.html. March 06, 2006.

Chen C, Puhakka JA, Ferguson JF. 1996. Transformations of 1,1,2,2-tetrachloroethane under methanogenic conditions. Environ Sci Technol 30:542-547.

Chen XM, Dallas CE, Muralidhara S, et al. 1993. Analysis of volatile C_2 haloethanes and haloethenes in tissues: Sample preparation and extraction. J Chromatogr 612:199-208.

9. REFERENCES

*Chieruttini ME, Franklin CS. 1976. The toxicology of tetrachloroethanes. Br J Pharmacol 57(3):421.

Chiou CT, Peters LJ, Freed VH. 1979. A physical concept of soil-water equilibria for nonionic organic compounds. Science 206:831-832.

Christensen JM, Rasmussen K, Koppen B. 1988. Automatic headspace gas chromatographic method for the simultaneous determination of trichloroethylene and metabolites in blood and urine. J Chromatogr 442:317-323.

Chu W, Chan KH. 2000. The predication of partitioning coefficients for chemicals causing environmental concern. Sci Total Environ 248:1-10.

Class T, Ballschmiter K. 1986. Chemistry of organic traces in air. VI: Distribution of chlorinated Cl-C4 hydrocarbons in air over the northern and southern Atlantic Ocean. Chemosphere 15:413-427.

Class T, Ballschmiter K. 1987. Global baseline pollution studies. X. Atmospheric halocarbons: Global budget estimations for tetrachloroethene, 1,2-dichloroethane, 1,1,1,2-tetrachloroethane, hexachloroethane, and hexachlorobutadiene. Estimation of the hydroxyl radical concentrations in the troposphere of the northern and southern hemispheres. Fresenius' Z Anal Chem 327:198-204.

Clewell HJ III, Andersen ME. 1985. Risk assessment extrapolations and physiological modeling. Toxicol Ind Health 1(4):111-131.

Colacci A, Grilli S, Lattanzi G, et al. 1987. The covalent binding of 1,1,2,2-tetrachloroethane to macromolecules of rat and mouse organs. Teratog Carcinog Mutagen 7:465-474.

Colacci A, Perocco P, Bartoli S, et al. 1992. Initiating activity of 1,1,2,2-tetrachlorethane in two-stage BALB/c 3T3 cell transformation. Cancer Lett 64:145-153.

Colacci A, Perocco P, Vaccari M, et al. 1990. In vitro transformation of BALB/c 3T3 cells by 1,1,2,2-tetrachloroethane. Jpn J Cancer Res 81:786-792.

Colacci A, Vaccari M, Perocco P, et al. 1996. Enhancement of BALB/c 3T3 cells transformation by 1,2-dibromoethane promoting effect. Carcinogenesis 17(2):225-231.

Cole RH, Frederick RE, Healy RP, et al. 1984. Preliminary findings of the priority pollutant monitoring project of the Nationwide Urban Runoff Program. Journal WPCF 56(7):898-908.

Comba ME, Kaiser KLE. 1983. Determination of volatile contaminants at the ng 1-1 level in water by capillary gas chromatography with electron capture detection. Int J Environ Anal Chem 16:17-31.

Cooper WJ, Mehran M, Riusech DJ, et al. 1987. Abiotic transformations of halogenated organics. 1. Elimination reaction of 1,1,2,2-tetrachloroethane and formation of 1,1,2-trichloroethene. Environ Sci Technol 21:1112-1114.

Cottalasso D, Bellocchio A, Domenicotti C, et al. 1998. 1,1,2,2-Tetrachloroethane-induced early decrease of dolichol levels in rat liver microsomes and golgi apparatus. J Toxicol Environ Health A 54:133-144.

9. REFERENCES

Cox RD. 1983. Sample collection and analytical techniques for volatile organics in air. In: Measurement and monitoring of non-criteria (toxic) contaminants in air. Pittsburgh, PA: Air Pollution Control Association, 101-112.

Coyer HA. 1944. Tetrachloroethane poisoning. Ind Med 13:230-233.

Cramer PH, Boggess KE, Hosenfeld JM, et al. 1988. Determination of organic chemicals in human whole blood: Preliminary method development for volatile organics. Bull Environ Contam Toxicol 40:612-618.

Crebelli R, Benigni R, Franekic J, et al. 1988. Induction of chromosome malsegregation by halogenated organic solvents in Aspergillus nidulans: Unspecific or specific mechanism? Mutat Res 201:401-411.

Daft JL. 1989. Determination of fumigants and related chemicals in fatty and nonfatty foods. J Agric Food Chem 37:560-564.

Daniel FB, DeAngelo AB, Stober JA, et al. 1992. Hepatocarcinogenicity of chloral hydrate, 2-chloroacetaldehyde, and dichloroacetic acid in male B6C3F1 mouse. Fundam Appl Toxicol 19:159-168.

DeAngelo AB, Daniel FB, Most BM, et al. 1996. The carcinogenicity of dichloroacetic acid in the male Fischer 344 rat. Toxicology 114:207-221.

DeAngelo AB, Daniel FB, Stober JA, et al. 1991. The carcinogenicity of dichloroacetic acid in the male B6C3F1 mouse. Fundam Appl Toxicol 16:337-347.

DeAngelo AB, George MH, House DE. 1999. Hepatocarcinogenicity in the male B6C3F1 mouse following a life-time exposure to dichloroacetic acid in the drinking water: Dose-response determination and modes of action. J Toxicol Environ Health 58:485-507.

DeAngelo AB, Herren-Freund S, Perreira MA, et al. 1986. Species sensitivity of the induction of peroxisome proliferation by trichloroethylene and its metabolites. Toxicologist 6:113.

Deguchi T. 1972. [A fundamental study of the threshold limit values for solvent mixtures in the air--Effects of single and mixed chlorinated hydrocarbons upon the level of serum transaminases in rats.] Osaka City Med J 21:187-209. (Japanese)

DeMarini DM, Brooks HG. 1992. Induction of phophage lambda by chlorinated organics: Detection of some single-species/single-site carcinogens. Environ Mol Mutagen 19:98-111.

DOT. 2005. Purpose and use of hazardous materials table. List of marine pollutants. U.S. Department of Transportation. Code of Federal Regulations. 49 CFR 172.101, Appendix B. http://a257.g.akamaitech.net/7/257/2422/09nov20051500/edocket.access.gpo.gov/cfr_2005/octqtr/pdf/49cfr172.101.pdf. January 08, 2008.

Dow. 1944. The toxicity of tetrachloroethane. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0517047.

Driscoll NM, Duffy H, Pappas S, et al. 1987. Analysis for purgeable organics in water by capillary BC/PID-ElCD. J Chromatogr Sci 25:369-375.

Ellenhorn MJ, Schonwald S, Ordog G, et al. 1997. 1,1,2,2-Tetrachloroethane. Ellenhorn's medical toxicology: Diagnosis and treatment of human poisoning. 2nd ed. Baltimore, MD: Williams and Wilkins, 1436-1440.

Elliott JM. 1933. Report of a fatal case of poisoning by tetrachloroethane. J Army Med Corp 60:373-374.

EPA. 1977. Monitoring to detect previously unrecognized pollutants in surface waters. Appendix: Organic analysis data. Washington, DC: U.S. Environmental Protection Agency. EPA560677015. (Appendix: EPA560677OlSA).

EPA. 1979. Water-related environmental fate of 129 priority pollutants-Volume III. Washington, DC: U.S. Environmental Protection Agency. EPA440479029B.

EPA. 1980. Survey of the Huntington and Philadelphia river water supplies for purgeable organic contaminants. Annapolis, MD: U.S. Environmental Protection Agency, EPA903981003.

EPA. 1982a. Method 624. Purgeables. In: Test methods. Methods for organic chemical analysis of municipal and industrial wastewater. Cincinnati, OH: U.S. Environmental Protection Agency, Environmental Monitoring and Support Laboratory.

EPA. 1982b. Method 5030. Purge-and-trap method. In: Test methods for evaluating solid waste. Physical/Chemical methods. SW-846. 2nd ed. Washington, DC: U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response.

EPA. 1984a. Method 601. Purgeable halocarbons. In: Guidelines establishing test procedures for the analysis of pollutants under the Clean Water Act; final rule and interim final rule and proposed rule. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 136.

EPA. 1984b. Method T01. Method for the determination of volatile organic compounds in ambient air using Tenaz adsorption and gas chromatography/ mass spectrometry (GC/MS). In: Compendium of methods for determination of toxic organic compounds in ambient air. Research Triangle Park, NC: U.S. Environmental Protection Agency, Environmental Monitoring Systems Laboratory, Office of Research and Development. EPA600484041.

EPA. 1984c. Compendium method T0-14. The determination of volatile organic compounds (VOCs) in ambient air using Summa passivated canister sampling and gas chromatographic analysis. In: Compendium of methods for determination of toxic organic compounds in ambient air. Research Triangle Park, NC: U.S. Environmental Protection Agency, Environmental Monitoring Systems Laboratory, Office of Research and Development. EPA600484041. http://www.epa.gov/ttn/amtic/files/ambient/airtox/to-14ar.pdf. May 10, 2006.

EPA. 1986a. Method 8240. Gas chromatography/mass spectrometry for volatile organics. In: Test methods for evaluating solid waste: Volume 1B: Laboratory manual physical/chemical methods. SW-846. 3rd ed. Washington, DC: U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response.

EPA. 1986b. Method 8010. Halogenated volatile organics. In: Test methods for evaluating solid waste. Volume 1B: Laboratory manual physical/chemical methods. SW-846. 3rd ed. Washington, DC: U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response.

EPA. 1986c. Method 524.1. Volatile organic compounds in water by purge and trap gas chromatography/mass spectrometry. In: Methods for the determination of organic compounds in finished drinking water and raw source water. Cincinnati, OH: U.S. Environmental Protection Agency, Environmental Monitoring and Support Laboratory.

EPA. 1986d. Method 524.2. Volatile organic compounds in water by purge and trap capillary column gas chromatography/mass spectrometry. In: Methods for the determination of organic compounds in finished drinking water and raw source water. Cincinnati, OH: U.S. Environmental Protection Agency, Environmental Monitoring and Support Laboratory.

EPA. 1987. Statement of work for organic analysis: multimedia, multiconcentration. Washington, DC: U.S. Environmental Protection Agency, U.S. EPA Contract Laboratory Program.

EPA. 1988a. Method 502.1. Volatile halogenated organic compounds in water by purge and trap gas chromatography. In: Methods for the determination of organic compounds in drinking water. Cincinnati OH: U.S. Environmental Protection Agency, Environmental Monitoring Systems Laboratory, Office of Research and Development. Revision 2.0. EPA600488039.

EPA. 1988b. Method 502.2. Volatile organic compounds in water by purge and trap capillary column gas chromatography with photoionization and electrolytic conductivity detectors in series. In: Methods for the determination of organic compounds in drinking water. Cincinnati OH: U.S. Environmental Protection Agency, Environmental Monitoring Systems Laboratory, Office of Research and Development. Revision 2.0. EPA600488039.

EPA. 1988c. National ambient volatile organic compounds (VOCs) data base update. Research Triangle Park, NC: U.S. Environmental Protection Agency, Atmospheric Sciences Research Laboratory. EPA600388010a.

EPA. 1989. Methods 508, 501.1, 502.2. Methods for the determination of organic compounds in drinking water. Cincinnati, OH: U.S. Environmental Protection Agency. EPA600484039.

EPA. 1990. Interim methods for development of inhalation reference concentrations. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Office of Research and Development, Environmental Criteria and Assessment Office. EPA600890066A.

EPA. 1995. Toxic chemical release inventory reporting Form R and instructions. Washington, DC: U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics. EPA745K95051.

EPA. 1996a. Method 8260B: Volatile organic compounds by gas chromatography/mass spectrometry (GC/MS). In: SW-846 online: Test methods for evaluating solid waste, physical/chemical methods. Washington, DC: U.S. Environmental Protection Agency, Office of Solid Waste. http://www.nemi.gov. April 3, 2006.

EPA. 1996b. Method 8021B: Aromatic and halogenated volatiles by gas chromatography using photoionization and/or electrolytic conductivity detectors. In: SW-846 online: Test methods for evaluating solid waste, physical/chemical methods. Washington, DC: U.S. Environmental Protection Agency, Office of Solid Waste. http://www.epa.gov/epaoswer/hazwaste/test/pdfs/8021b.pdf. April 05, 2006.

EPA. 1997. Special report on environmental endocrine disruption: An effects assessment and analysis. Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. EPA630R96012.

EPA. 2000. Benchmark dose technical guidance document [external review draft]. EPA630R00001. Washington, DC: U.S. Environmental Protection Agency. http://www.epa.gov/iris/backgr-d.htm. August 1, 2006.

EPA. 2001a. Method 1624. Volatile organic compounds by isotope dilution GC/MS. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR Part 136, Appendix A, 275-287.

EPA. 2001b. Unregulated contaminant monitoring program. Washington, DC: U.S. Environmental Protection Agency. http://www.epa.gov/safewater/ucmr/ucm_rounds_1-2.html. March 25, 2006.

EPA. 2002. Child-specific exposure factors handbook. Washington, DC: U.S. Environmental Protection Agency, National Center for Environmental Assessment, Office of Research and Development. EPA600P00002B.

EPA. 2003. National primary drinking water standards. Washington, DC: U.S. Environmental Protection Agency, Office of Ground Water and Drinking Water. EPA816F03016. http://www.epa.gov/safewater/mcl.html. March 07, 2006.

EPA. 2005. Toxic chemical release inventory reporting forms and instructions: Revised 2004 version. Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986). U.S. Environmental Protection Agency. Office of Environmental Information. EPA260B05001.

EPA. 2006i. 2006 Edition of the drinking water standards and health advisories. Washington, DC: Office of Water, U.S. Environmental Protection Agency. EPA822R06013. http://www.epa.gov/waterscience/criteria/drinking/dwstandards.pdf. April 11, 2007.

EPA. 2006h. Acute Exposure Guideline Levels (AEGLs) Washington, DC: Office of Pollution Prevention and Toxics. U.S. Environmental Protection Agency. http://www.epa.gov/oppt/aegl/chemlist.htm. March 14, 2006.

EPA. 2006b. Designation of hazardous substances. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 302.4. http://a257.g.akamaitech.net/7/257/2422/22jul20061500/edocket.access.gpo.gov/cfr_2006/julqtr/pdf/40cfr302.4.pdf. January 08, 2008.

EPA. 2006a. Hazardous air pollutants. Clean Air Act. U.S. Environmental Protection Agency. United States Code. 42 USC 7412. http://www.epa.gov/ttn/atw/orig189.html. March 07, 2006.

EPA. 2006k. Identification and listing of hazardous waste. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 261, Appendix VIII. http://www.epa.gov/epacfr40/chapt-I.info/chi-toc.htm. March 08, 2006.

EPA. 2006j. National recommended water quality criteria. Washington, DC: U.S. Environmental Protection Agency, Office of Water, Office of Science and Technology. http://www.epa.gov/waterscience/criteria/nrwqc-2006.pdf. January 08, 2008.

EPA. 2006c. Toxic chemical release reporting: Community right-to-know. Chemicals and chemical categories to which this part applies. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 372.65. http://a257.g.akamaitech.net/7/257/2422/22jul20061500/edocket.access.gpo.gov/cfr_2006/julqtr/pdf/40cfr372.65.pdf. January 08, 2008.

EPA. 2006d. RCRA orientation manual 2006; Resource Conservation and Recovery Act. U.S. Environmental Protection Agency. http://www.epa.gov/epaoswer/general/orientat/. August 16, 2006.

EPA. 2006e. Protection of the environment: Land disposal restrictions. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 268. http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?c=ecfr&sid=d85c2f33b4eb3198d0bb904161bde684&rgn=div5&view=text&node=40:26.0.1.1.3&idno=40. August 16, 2006.

EPA. 2006f. 1,1,2,2-Tetrachloroethane. Modernized STORET system: Regular results by geographic location (stormodb): Characteristic search by CAS number. U.S. Environmental Protection Agency. http://www.epa.gov/storet/dbtop.html. April 06, 2006.

EPA. 2006g. Water quality standards. Toxics criteria for those states not complying with Clean Water Act section 303(c)(2)(B). U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 131.36. http://www.epa.gov/epacfr40/chapt-I.info/chi-toc.htm. March 08, 2006.

Eriksson C, Brittebo EB. 1991. Epithelial binding of 1,1,2,2-tetrachloroethane in the respiratory and upper alimentary tract. Arch Toxicol 65:10-14.

FDA. 2005a. Beverages. Bottled water. Code of Federal Regulations. 21 CFR 165.110. U.S. Food and Drug Administration. http://a257.g.akamaitech.net/7/257/2422/01apr20051500/edocket.access.gpo.gov/cfr_2005/aprqtr/pdf/21cfr165.110.pdf. January 08, 2008.

FDA. 2005b. Total diet study. Washington, DC: U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition. http://www.cfsan.fda.gov/~comm/tds-toc.html. March 18, 2006.

FEDRIP. 2006. 1,1,2,2 Tetrachloroethane. Federal Research in Progress database. Springfield, VA: National Technical Information Service.

Ferguson JF, Pietari JM. 2000. Anaerobic transformations and bioremediation of chlorinated solvents. Environ Pollut 107(2):209-215.

Fisher J, Mahle D, Bankston L, et al. 1997. Lactational transfer of volatile chemicals in breast milk. Am Ind Hyg Assoc J 58(6):425-431.

Fomon SJ. 1966. Body composition of the infant: Part I: The male reference infant. In: Falkner F, ed. Human development. Philadelphia, PA: WB Saunders, 239-246.

Fomon SJ, Haschke F, Ziegler EE, et al. 1982. Body composition of reference children from birth to age 10 years. Am J Clin Nutr 35:1169-1175.

Forbes G. 1943. Tetrachloroethane poisoning. Br Med J 1:348-350.

Franke C, Studinger G, Berger G, et al. 1994. The assessment of bioaccumulation. Chemosphere 29(7):1501-1514.

Galloway SM, Armstrong MJ, Reuben C, et al. 1987. Chromosome aberrations and sister chromatid exchange in Chinese hamster ovary cells: Evaluations of 108 chemicals. Environ Mol Mutagen 10:1-175.

Gargas ML, Andersen ME. 1989. Determining kinetic constants of chlorinated ethane metabolism in the rat from rates of exhalation. Toxicol Appl Pharmacol 99:344-353.

Gargas ML, Burgess RJ, Voisard DE, et al. 1989. Partition coefficients of low-molecular-weight volatile chemicals in various liquids and tissues. Toxicol Appl Pharmacol 98:87-99.

Gianti SJ Jr, Harkov R, Bozzelli JW. 1984. Monitoring volatile organic compounds at hazardous and sanitary landfills in New Jersey. Presented 77th Annual Meeting of the Air Pollution Control Association, Paper No. 84-3.7, June 24-29, San Francisco, CA. Pittsburgh, PA: Air Pollution Control Association.

Ginsberg G, Hattis D, Sonawane B, et al. 2002. Evaluation of child/adult pharmacokinetic differences from a database derived from the therapeutic drug literature. Toxicol Sci 66:185-200.

Ginsberg G, Hattis D, Sonawane B. 2004. Incorporating pharmacokinetic differences between children and adults in assessing children's risk to environmental toxicants. Toxicol Appl Pharmacol 198:164-183.

Giwercman A, Carlsen E, Keiding N, et al. 1993. Evidence for increasing incidence of abnormalities of the human testis: A review. Environ Health Perspect Suppl 101(2):65-71.

Gobbato F, Bobbio G. 1968. [Investigation of the cardiovascular function in 75 industrial workers employed in the production of tetrachloroethane, trichloroethylene and perchloroethylene.] Securitias 53:43-63. (Italian)

Gohlke R, Schmidt P. 1972. [Subacute action of low concentrations of chlorinated ethanes with and without additional ethanol treatment in the rat.] Int Arch Arbeitsmed 30:299-312. (German)

Gohlke R, Schmidt P, Bahmann H. 1977. [1,1,2,2-Tetrachloroethane and heat stress in animal experiment. Morphological results.] Z Gesamte Hyg IHRE Grenzgeb 20:278-282. (German)

Goldfrank LR, Flomenbaum NE, Lewin NA, et al. 2002. Hydrocarbons. In: Goldfrank's toxicologic emergencies. New York, NY: McGraw Hill, 1303-1322.

Guengerich FP, Kim D-H, Iwasaki M. 1991. Role of human cytochrome P-450 IIE1 in the oxidation of many low molecular weight cancer suspects. Chem Res Toxicol 4:168-179.

Guidotti M, Onorati B, Lucarelli E, et al. 2001. Determination of chlorinated solvents in exhaled air, urine, and blood of subjects exposed in the workplace using SPME and GC-MS. Am Clin Lab 20(4):23-26.

Gupta KC, Ulsamer AG, Gammage R. 1984. Volatile organic compounds in residential air: Levels, sources and toxicity. Proc APCA Annual Meeting 77:1-9.

Guzelian PS, Henry CJ, Olin SS, eds. 1992. Similarities and differences between children and adults: Implications for risk assessment. Washington, DC: International Life Sciences Institute Press.

Haag WR, Mill T. 1988. Effect of a subsurface sediment on hydrolysis of haloalkanes and epoxides. Environ Sci Technol 22:658-663.

Haddad LM, Shannon MW, Winchester JF. 1998. Chlorinated hydrocarbons. In: Clinical management of poisoning and drug overdose. Philadelphia, PA: WB Saunders Company, 931-939.

Hallen RT, Pyne JW Jr, Molton PM. 1986. Transformation of chlorinated ethenes and ethanes by anaerobic microorganisms. In: American Chemical Society Division of Environmental Chemistry: 192nd National Meeting, Anaheim, California, September 7-12, 1986. Washington, DC: American Chemical Society, 344-346.

Halpert J. 1981. Covalent modification of lysine during the suicide inactivation of rat liver cytochrome P-450 by chloramphenicol. Biochem Pharmacol 30:875-881.

Halpert J. 1982. Cytochrome P-450 dependent covalent binding of 1,1,2,2-tetrachloroethane in vitro. Drug Metab Dispos 10:465-468.

Halpert J, Neal RA. 1981. Cytochrome P-450 metabolism of 1,1,2,2-tetrachloroethane to dichloroacetic acid in vitro. Biochem Pharmacol 30:1366-1368.

Halpert JR, Balfour C, Miller NE, et al. 1986. Dichloromethyl compounds as mechanism-based inactivators of rat liver cytochromes P-450 in vitro. Mol Pharmacol 30:19-24.

Hamilton A. 1917. Military medicine and surgery. J Am Med Assoc 69:2037-2039.

Hanley TR, Quast JF, Schumann AM. 1988. The metabolism and hepatic macromolecular interactions of 1,1,2,2-tetrachloroethane (TCE) in mice and rats. Dow Chemical Company. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0514187.

Hansch C, Leo A, Hoekman D. 1995. 1,1,2,2-Tetrachloroethane. In: Exploring QSAR hydrophobic, electronic, and steric constants. Washington, DC: American Chemical Society, 4.

Harkov R, Katz R, Bozzelli J, et al. 1981. Toxic and carcinogenic air pollutants in New Jersey volatile organic substances. In: McGovern JJ, ed. Proceedings from International Technical Conference Toxic Air Contamination, 1980. Pittsburgh, PA: Air Pollution Control Association, 104-119.

Harkov R, Kebbekus B, Bozzelli JW, et al. 1983. Measurement of selected volatile organic compounds at three locations in New Jersey during the summer season. JAPCA 33:1177-1183.

Harkov R, Kebbekus B, Bozzelli JW. 1987. Volatile organic compounds at urban sites in New Jersey. In: Lioy PJ, Daisey JM, eds. Toxic air pollutants. Chelsea, MI: Lewis Publishers, 69-88.

Harte J, Holdren C, Schneider R, et al. 1991. Toxics A to Z: A guide to everyday pollution hazards. Berkeley, CA: University of California Press, 303-305, 413-415, 418-422, 430-433.

Hartwell TD, Pellizzari ED, Penritt RL, et al. 1987. Results from the total exposure assessment methodology (TEAM) study in selected communities in northern and southern California. Atmos Environ 21:1995-2004.

Haworth S, Lawlor T, Mortelmans K, et al. 1983. Salmonella mutagenicity test results for 250 chemicals. Environ Mutagen 5:3-142.

HazDat. 2008. 1,1,2,2-tetrachloroethane. HazDat Database: ATSDR's Hazardous Substance Release and Health Effects Database. Atlanta, GA: Agency for Toxic Substances and Disease Registry. http://www.atsdr.cdc.gov/hazdat.html. June 5, 2008.

Hemmings HC Jr, Akabas MH, Goldstein PA, et al. 2005. Emerging molecular mechanisms of general anesthetic action. Trends Pharmacol Sci 26(10):503-510.

Hepple RA. 1927. An unusual case of poisoning. J Army Med Corp 49:442-445.

Herren-Freund SL, Pereira MA, Khoury DK, et al. 1987. The carcinogenicity of trichloroethylene and its metabolites, trichloroacetic acid and dichloroacetic acid, in mouse liver. Toxicol Appl Pharm 90:183-189.

Hiatt MH. 1983. Determination of volatile organic compounds in fish samples by vacuum distillation and fused silica capillary gas chromatography/mass spectrometry. Anal Chem 55:506-516.

Hoel DG, Davis DL, Miller AB, et al. 1992. Trends in cancer mortality in 15 industrialized countries, 1969-1986. J Natl Cancer Inst 84(5):313-320.

*Horiguchi S, Morioka S, Utsunomiya T, et al. 1964. A survey of the actual conditions of artificial pearl factories with special reference to the work using tetrachloroethane. Jpn J Ind Health 6:251-256.

Horiuchi K, Horiguchi S, Hashimoto K, et al. 1962. Studies on the industrial tetrachloroethane poisoning. Osaka City Medical J 8:29-38.

Horvath AL, Getzen FW, Maczynska Z. 1999. IUPAC-NIST solubility data series 67. Halogenated ethanes and ethenes with water. J Phys Chem Ref Data 28:395-627.

Horvath M, Frantik E. 1973. To the relative sensitivity of nervous functions and behavior to nonspecific effects of foreign substances. Activ Nerv Super 15:25-27.

HSDB. 1996. Online. Hazardous Substance Data Bank. National Library of Medicine, Bethesda, MD.

HSDB. 2006. 1,1,2,2-tetrachloroethane. Hazardous Substances Data Bank. National Library of Medicine. http://toxnet.nlm.nih.gov. March 30, 2006.

IARC. 1979. 1,1,2,2-Tetrachloroethane. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans: Some halogenated hydrocarbons. Lyon, France: International Agency for Research on Cancer, World Health Organization 20:477-489.

IARC. 2004. Overall evaluations of carcinogenicity to humans: As evaluated in IARC Monographs volumes 1-82 (at total of 900 agents, mixtures and exposures). Lyon, France: International Agency for Research on Cancer. http://www-cie.iarc.fr/monoeval/crthall.html. March 08, 2006.

Ikeda M, Ohtsuji H. 1972. Comparative study of the excretion of Fujiwara reaction-positive substances in urine of humans and rodents given trichloro-or tetrachloro-derivatives of ethane and ethylene. Br J Ind Med 29:99-184.

IRIS. 2006. 1,1,2,2 Tetrachloroethane. Washington, DC: Integrated Risk Information System, U.S. Environmental Protection Agency. http://www.epa.gov/iris/subst/index.html. March 08, 2006.

IUR. 2002. Inventory update rule. Toxic Substance Control Act (TSCA) Inventory Update Database. Washington, DC: U.S. Environmental Protection Agency. http://www.epa.gov/opt/uiru/iur02/index.htm. March 22, 2006.

Jafvert CT, Wolfe NL. 1987. Degradation of selected halogenated ethanes in anoxic sediment-water systems. Environ Toxicol Chem 6:827-837.

Jakobson I, Wahlberg JE, Holmberg B, et al. 1982. Uptake via the blood and elimination of 10 organic solvents following epicutaneous exposure of anesthetized guinea pigs. Toxicol Appl Pharmacol 63:181-187.

Jeney E, Bartha F, Kondor L, et al. 1957. [Prevention of industrial tetrachloroethane intoxication--Part III.] Egeszsegtudomany 1:155-164. (Hungarian)

Johanson CE. 1980. Permeability and vascularity of the developing brain: Cerebellum vs cerebral cortex. Brain Res 190:3-16.

Johansson I, Ekstrom G, Scholte B, et al. 1988. Ethanol-, fasting- and acetone-inducible cytochromes P-450 in rat liver. Biochemistry 27:1925-1934.

*Kanada M, Miyagawa M, Sato M, et al. 1994. Neurochemical profile of effects of 28 neurotoxic chemicals on the central nervous system in rats (1). Effects of oral administration on brain contents of biogenic amines and metabolites. Ind Health 32:145-164.

Khourey CJ, Mohr ET, Gifford G, et al. 1984. Purgeable organic compounds in northeast Ohio groundwater. Trace Subst Environ Health 18:397-403.

Kincannon DF, Weinert A, Padorr R, et al. 1983. Predicting treatability of multiple organic priority pollutant wastewater from single-pollutant treatability studies. In: Bell MR, ed. Proceedings 37th Industrial Waste Conference. Ann Arbor, MI: Ann Arbor Science, 641-650.

*Kitchin KT, Brown JL, Kulkarni AP. 1992. Predictive assay for rodent carcinogenicity using in vivo biochemical parameters: Operation characteristics and complementarity. Mutat Res 266(2):253-272.

Klaassen, CD. 1996. Casarett & Doull's toxicology: The basic science of poisons. 5th ed. New York, NY: McGraw-Hill, 750-751.

Klečka GM, Gonsior SJ. 1983. Nonenzymatic reductive dechlorination of chlorinated methane and ethanes in aqueous solution. Dow Chemical Company. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8. OTS206368.

Koelsch F. 1915. Industrial poisonings by celluloid varnishes in the airplane industry. Muench Medizin Wochensch 62:1567-1569.

Koizumi A, Kumai M, Ikeda M. 1982. Enzymatic formation of an olefin in the metabolism of 1,1,2,2-tetrachloroethane: An in vitro study. Bull Environ Contam Toxicol 29:562-565.

Komori M, Nishio K, Kitada M, et al. 1990. Fetus-specific expression of a form of cytochrome P-450 in human livers. Biochemistry 29:4430-4433.

Konasewich D, Traversy W, Zar H. 1978. Great Lakes water quality status report on organic and heavy metal contaminants in the Lakes Erie, Michigan, Huron, and Superior basins. Windsor, Ontario: Great Lakes Water Quality Board, 26-27, 112.

Konietzko H. 1984. Chlorinated ethanes: Sources, distribution, environmental impact, and health effects. Hazard Assessment of Chemicals Current Developments 3:401-448.

Koppel C, Armdt I, Arendt U, et al. 1985. Acute tetrachloroethylene poisonings: Blood elimination kinetics during hyperventilation therapy. Clin Toxicol 23:103-115.

Koppen B, Dalgaard L, Christensen JM. 1988. Determination of trichloroethylene metabolites in rat liver homogenate using headspace gas chromatography. J Chromatog 442:325-332.

Krill RM, Sonzogni WC. 1986. Chemical monitoring of Wisconsin's groundwater. J Am Water Works Assoc 78:70-75.

Krishnan K, Andersen ME. 1994. Physiologically based pharmacokinetic modeling in toxicology. In: Hayes AW, ed. Principles and methods of toxicology. 3rd ed. New York, NY: Raven Press, Ltd., 149-188.

Krishnan K, Andersen ME, Clewell HJ III, et al. 1994. Physiologically based pharmacokinetic modeling of chemical mixtures. In: Yang RSH, ed. Toxicology of chemical mixtures: Case studies, mechanisms, and novel approaches. San Diego, CA: Academic Press, 399-437.

Kronevi T, Wahlberg JE, Holmberg B. 1981. Skin pathology following epicutaneous exposure to seven organic solvents. Int J Tissue React 3:21-30.

Krost KJ, Pellizzari ED, Walburn SG, et al. 1982. Collection and analysis of hazardous organic emissions. Anal Chem 54:810-817.

Kulinskaya IL, Verlinskaya RV. 1972. [Comparative effect of low concentration of di-, tetra- and pentachloroethane on the blood acetylcholine system.] Gig Tr Prof Zabol 16:56-58. (Russian)

Laass W. 1973a. [Suitability of castor oil treating acute oral poisonings with organic solvents. Pharmazie 28:684-685. (German)

Laass W. 1973b. [Animal experimental studies on the suitability of mineral oil in acute oral poisoning with organic solvents.] Pharmazie 28:65-66. (German)

Laass W. 1974a. [Animal studies on the action of milk in acute oral poisonings with organic solvents.] Pharmazie 29:729. (German)

Laass W. 1974b. [Suitability of using activated charcoal for the treatment of acute oral poisoning with organic solvents.] Pharmazie 29:728-729. (German)

LaRegina J, Bozzelli JW, Harkov R, et al. 1986. Volatile organic compounds at hazardous waste sites and a sanitary landfill in New Jersey. An up-to-date review of the present situation. Environ Prog 5:18-27.

Lazarew NW. 1929. [The narcotic effect of the vapors of the chloride derivatives of methane, ethane and ethylene.] Arch Exp Path Pharmakol 141:19-24. (German)

Lee MD, Mazierski PF, Buchanan RJ, et al. 1995. Intrinsic in situ anaerobic biodegradation of chlorinated solvents at an industrial landfill. In: Hinchee RE, ed. Intrinsic bioremediation. 3rd ed. Columbus, OH: Battelle Press, 205-222.

Leeder JS, Kearns GL. 1997. Pharmacogenetics in pediatrics: Implications for practice. Pediatr Clin North Am 44(1):55-77.

Lehmann KB. 1911. [Experimental studies on the influence of technology and hygienically important gases and vapors on the organism (XVI-XXIII)-Chlorinated aliphatic hydrocarbons and considerations on the one-stage and two-stage toxicity of volatile products.] Arch Hyg 74:1-3,24-28,46-60. (German)

Lehmann KB, Schmidt-Kehl L. 1936. [Study of the 13 most important chlorohydrocarbons from the standpoint of industrial hygienics.] Arch Hyg 116:132-200. (German)

Leighton DT Jr, Calo JM. 1981. Distribution coefficients of chlorinated hydrocarbons in dilute air-water systems for groundwater contamination applications. J Chem Eng Data 26:382-385.

Lesage S. 1991. Characterization of groundwater contaminants using dynamic thermal stripping and adsorption/ thermal desorption - GC-MS. Fresenius J Anal Chem 339:516-527.

Leung H-W. 1993. Physiologically-based pharmacokinetic modeling. In: Ballentyne B, Marrs T, Turner P, eds. General and applied toxicology. Vol. 1. New York, NY: Stockton Press, 153-164.

Lewis RJ. 2001. Hawley's condensed chemical dictionary. 14th ed. New York, NY: John Wiley & Sons, Inc., 1079.

Lide DR, ed. 2005. CRC handbook of chemistry and physics. 86th ed. Boca Raton FL: CRC Press, 3-470, 3-471.

Lilliman B. 1949. Suggested mechanism of poisoning by liquid tetrachloroethane. Analyst 74:510-511.

Lioy PJ, Daisey JM, Greenberg A, et al. 1985. A major wintertime (1983) pollution episode in northern New Jersey: Analysis of the accumulation and spatial distribution of inhalable particulate matter, extractable organic matter and other species. Atmos Environ 19:429-436.

Livingston, AL. 1978. Forage plant estrogens. J Toxicol Environ Health 4:301-324.

Lobo-Mendonca R. 1963. Tetrachloroethane - A survey. Br J Ind Med 20:51-56.

Lopez-Avila V, Heath N, Hu A. 1987. Determination of purgeable halocarbons and aromatics by photoionization and Hall electrolytic conductivity detectors connected in series. J Chromatog Sci 25:356-363.

Lorah MM, Olsen LD. 1999a. Natural attenuation of chlorinated volatile organic compounds in a freshwater tidal wetland: Field evidence of anaerobic biodegradation. Water Resour Res 35(12):3811-3827.

Lorah MM, Olsen LD. 1999b. Degradation of 1,1,2,2-tetrachloroethane in a freshwater tidal wetland: Fields and laboratory evidence. Environ Sci Technol 33:227-234.

Lorah MM, Voytek MA. 2004. Degradation of 1,1,2,2-tetrachloroethane and accumulation of vinyl chloride in wetland sediment microcosms and in situ porewater: Biogeochemical controls and associations with microbial communities. J Contam Hydrol 70(1-2):117-145.

Mackay D, Shiu WY. 1981. A critical review of Henry's Law constants for chemicals of environmental interest. J Phys Chem Ref Data 10(4):1175-1199.

Mant AK. 1953. Acute tetrachlorethane poisoning. A report on two fatal cases. Br Med J 655-656.

Matz G, Kesners P. 1993. Spray and trap method for water analysis by thermal desorption gas chromatography/mass spectrometry in field applications. Anal Chem 65:2366-2371.

Mayr U, Butsch A, Schneider S. 1992. Validation of two in vitro test systems for estrogenic activities with zearalenone, phytoestrogens and cereal extracts. Toxicology 74:135-149.

Melton RG, Coleman WE, Slater RW et al. 1981. Comparison of Grob closed-loop stripping analysis with other trace organic methods. In: Keith LH, ed. Advances in the identification & analysis of organic pollutants in water. Ann Arbor, MI: Ann Arbor Science, 597-673.

Meulenberg CJW, Vijverberg HPM. 2000. Empirical relations predicting human and rat tissue: Air partition coefficients of volatile organic compounds. Toxicol Appl Pharmacol 165(3):206-216.

Milman HA, Mitoma C, Tyson C, et al. 1984. Comparative pharmacokinetics/metabolism, carcinogenicity and mutagenicity of chlorinated ethanes and ethylenes (meeting abstract). Arbete och Halsa 29:19.

Milman HA, Story DL, Riccio ES, et al. 1988. Rat liver foci and in vitro assays to detect initiating and promoting effects of chlorinated ethanes and ethylenes. Ann NY Acad Sci 534:521-530.

Minot GR, Smith LW. 1921. The blood in tetrachloroethane poisoning. Arch Intern Med 28:687-702.

Mirsalis JC, Tyson CK, Steinmetz KL, et al. 1989. Measurement of unscheduled DNA synthesis and s-phase synthesis in rodent hepatocytes following in vivo treatment: Testing of 24 compounds. Environ Mol Mutagen 14:155-164.

Mitoma C, Steeger T, Jackson SE, et al. 1985. Metabolic disposition study of chlorinated hydrocarbons in rat and mice. Drug Chem Toxicol 3:183-194.

Mitoma C, Tyson CA, Riccio ES. 1984. Investigations of the species sensitivity and mechanism of carcinogenicity of halogenated hydrocarbons, final report. SRI International. Submitted to the U.S. Environmental Protection Agency under TSCA Section 4. OTS0509408.

Miyagawa M, Takasawa H, Sugiyama A, et al. 1995. The in vivo-in vitro replicative DNA synthesis (RDS) test with hepatocytes prepared from male B6C3F1 mice as an early prediction assay for putative nongenotoxic (Ames-negative) mouse hepatocarcinogens. Mutat Res 343:157-183.

Mohamed MF, Kang D, Aneja VP. 2002. Volatile organic compounds in some urban locations in United States. Chemosphere 47:863-882.

Montgomery JH, Welkom LM. 1990. Groundwater chemicals desk reference. Chelsea, MI: Lewis Publishers, 491-495.

Morgan A, Black A, Belcher DR. 1970. The excretion in breath of some aliphatic halogenated hydrocarbons following administration by inhalation. Ann Occup Hyg 13:219.

Morselli PL, Franco-Morselli R, Bossi L. 1980. Clinical pharmacokinetics in newborns and infants: Age-related differences and therapeutic implications. Clin Pharmacokin 5:485-527.

Mosesman NH, Sidisky LM, Corman SD. 1987. Factors influencing capillary analyses of volatile pollutants. J Chromatogr Sci 25:351-355.

Mouradian RF, Levine SP, Ke HQ, et al. 1991. Measurement of volatile organics at part per billion concentrations using a cold trap inlet and high speed gas chromatography. J Air Waste Manage Assoc 41:1067-1072.

Mudder TI, Musterman JL. 1982. Development of empirical structure biodegradability relationships and biodegradability testing protocol for volatile and slightly soluble priority pollutants. Presented before the Division of Environmental Chemistry of the American Chemical Society, Kansas City, MO, September 1982, 52-53.

*Nakajima T, Sato A. 1979. Enhanced activity of liver drug metabolizing enzymes for aromatic and chlorinated hydrocarbons following food deprivation. Toxicol Appl Pharmacol 50:549-556.

NARA. 2006. Code of federal regulations. Washington, DC: National Archives and Records Administration. http://www.access.gpo.gov/nara/cfr/cfr-table-search.html. March 20, 2006.

NAS/NRC. 1989. Biologic markers in reproductive toxicology. National Academy of Science, National Research Council. Washington, DC: National Academy Press, 15-35.

Navrotskiy VK, Kashin LM, Kulinskoya IL. 1971. [Comparative assessment of the toxicity of a number of industrial poisons when inhaled in low concentrations for prolonged periods.] Trudy S'ezda Gig Ukran 8:224-226. (Russian)

Naylor Dana Institute. 1983. DNA repair tests of 11 chlorinated hydrocarbon analogs final report EPA contract. Submitted to the U.S. Environmental Protection Agency under TSCA Section 4. OTS0509403.

NCI. 1976. Carcinogenesis bioassay of trichloroethylene (CAS No. 79-01-6). Bethesda, MD: National Cancer Institute, Division of Cancer Cause and Prevention, Carcinogenesis Program, Carcinogen Bioassay and Program Resources Branch. NCI-CG-TR-2, DHEW Publ. No. (NIH) 76-802.

NCI. 1977. Bioassay of tetrachloroethylene for possible carcinogenicity. Bethesda, MD: National Cancer Institute. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, DHEW Publ (NIH) 77-813.

NCI. 1978. Bioassay of 1,1,2,2-tetrachloroethane for possible carcinogenicity. National Cancer Institute. PB2774537, 90.

Nebert DW, Adesnik M, Coon MJ, et al. 1987. The P450 gene superfamily: Recommended nomenclature. DNA 6(1):1-11.

NEMI. 1997a. Method 6200B: Volatile organic compounds in water by purge and trap capillary-column GC/MS method. National Environmental Methods Index. U.S. Environmental Protection Agency. U.S. Geological Survey. http://www.nemi.gov. April 20, 2006.

NEMI. 1997b. Method 6200C: Volatile organic compounds in water by purge and trap capillary-column GC method. National Environmental Methods Index. U.S. Environmental Protection Agency. U.S. Geological Survey. http://www.nemi.gov. April 20, 2006.

NEMI. 2001. Method D5790: Standard test method for measurement of purgeable organic compounds in water by capillary column gas chromatography/mass spectrometry. National Environmental Methods Index. U.S. Environmental Protection Agency. U.S. Geological Survey. http://www.nemi.gov. April 20, 2006.

Nestmann ER, Lee EGH. 1983. Mutagenicity of constituents of pulp and paper mill effluent in growing cells of Saccharomyces cerevisiae. Mutat Res 119:273-280.

Nestmann ER, Lee EG-H, Matula TI, et al. 1980. Mutagenicity of constituents identified in pulp and paper mill effluents using the Salmonella mammalian-microsome assay. Mutat Res 79:203-212.

NIOSH. 1978. Toxicity data for establishing "immediately dangerous to life or health" (IDLH) values. Cincinnati, OH: National Institute for Occupational Safety and Health. PB87163531.

NIOSH. 1980. Tier II mutagenic screening of 13 NIOSH priority compounds, individual compound report, 1,1,2,2-tetrachloroethane, Report No 26. Cincinnati, OH: National Institute for Occupational Safety and Health. PB83149369.

NIOSH. 1992. Recommendations for occupational safety and health; Compendium of policy documents and statements. Cincinnati, OH: U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health, 124, 161-170.

NIOSH. 1994. Method 1019. Manual of analytical methods 1,1,2,2,-tetrachloroethane. 4th ed. Cincinnati, OH: U.S. Department of Health, Education, and Welfare, National Institute for Occupational Safety and Health.

NIOSH. 2005. 1,1,2,2 Tetrachloroethane. NIOSH pocket guide to chemical hazards. Atlanta, GA: National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention. http://www.cdc.gov/niosh/npg/. March 08, 2006.

NIOSH. 2006. 1,1,2,2-Tetrachloroethane. National occupational exposure survey 1981-83. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control. National Institute for Occupational Safety and Health, July 1, 1990.

Norman JE, Jr, Robinette CD, Fraumeni JF, Jr. 1981. The mortality experience of Army World War II chemical processing companies. J Occup Med 23:818-822.

NRC. 1993. Pesticides in the diets of infants and children. Washington, DC: National Academy Press. National Research Council.

NTP. 1986. National Toxicology Program--technical report series no. 311. Toxicology and carcinogenesis studies of tetrachloroethylene (perchloroethylene) (CAS No. 127- 18-4) in F344/N rats and B6C3Fl mice (inhalation studies). Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, NIH publication no. 86-2567.

NTP. 1990. National Toxicology Program--technical report series no. 243. Carcinogenesis studies of trichloroethylene (without epichlorohydrinin) (CAS No. 79-01-6) in Fischer-344/N rats and B6C3F1 mice (gavage studies). Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. NIH publication no. 90-1799.

NTP. 1991a. Report: Range finding studies: Developmental toxicity 1,1,2,2-tetrachloroethane when administered via feed in CD Sprague-Dawley rats. Prepared by Environmental Health Research and Testing, Inc., Contract NO1-ES-95249. National Toxicology Program. NTP-91-RF/DT-017. TRP 91029.

NTP. 1991b. Report: Range finding studies: Developmental toxicity 1,1,2,2-tetrachloroethane (repeat) then administered via feed in Swiss CD-1 mice. Prepared by Environmental Health Research and Testing, Inc., Contract NO1-ES-95249. National Toxicology Program. NTP-91-RF/DT-020. TRP 91069.

NTP. 1993a. 14-Day pilot gavage toxicity study of 1,1,2,2-tetrachloroethane in male F344/N rats. Prepared by TSI Mason Laboratories, Contract NO1-ES-15326. National Toxicology Program. MLI-NTP-13-93-13.

NTP. 1993b. 14-Day pilot gavage toxicity study of 1,1,2,2-tetrachloroethane in male F344/N rats. Prepared by TSI Mason Laboratories, Contract NO1-ES-15326. National Toxicology Program. MLI-NTP-1-93-1.

NTP. 1993c. 14-Day pilot dosed feed toxicity study of microencapsulated 1,1,2,2-tetrachloroethane in B6C3F1 mice. Prepared by TSI Mason Laboratories, Contract NO1-ES-15326. National Toxicology Program. MLI-NTP-9-93-9.

NTP. 1993d. 14-Day pilot gavage toxicity study of 1,1,2,2-tetrachloroethane in B6C3F1 mice. Prepared by TSI Mason Laboratories, Contract NO1-ES-15326. National Toxicology Program. MLI-NTP-10-93-10.

NTP. 1996. NTP technical report on renal toxicity studies of selected halogenated ethanes administered by gavage to F344/N rats. Research Triangle Park, NC: United States Department of Health and Human Services, Public Health Service National Institutes of Health, National Toxicology Program, 1-52.

NTP. 2004a. NTP technical report on the toxicity studies of 1,1,2,2-tetrachloroethane (CAS No. 79-34-5) administered in microcapsules in feed to F344/N rats and B6C3F1 mice. National Toxicology Program. Tox-49. http://ntp.niehs.nih.gov/ntp/htdocs/ST_rpts/tox049.pdf. October 04, 2004.

NTP. 2004b. Report on carcinogens. 11th ed. Research Triangle Park, NC: National Toxicology Program, Department of Health and Human Services. http://ntp-server.niehs.nih.gov/ntp/roc/toc11.html. January 11, 2008.

Ohio River Valley Sanitation Commission. 1980. Assessment of water quality conditions, Ohio River mainstream, 1978-1979. Cincinnati, OH: Ohio River Valley Water Sanitation Commission.

Omiecinski CJ, Remmel RP, Hosagrahara VP. 1999. Concise review of the cytochrome P450s and their roles in toxicology. Toxicol Sci 48:151-156.

O'Neil MJ, Smith A, Heckelman PE, et al., eds. 2001. Merck index: an encyclopedia of chemicals, drugs, and biologicals. 13th ed. Rahway NJ: Merck & Co., Inc., 1640.

Ono Y, Kobayashi U, Somiya I, et al. 1996. Evaluation of DNA damage by active oxygen induced by organochlorine compounds and nitroarenes. Mizu Kankyo Gakkaishi 19:87-877.

OSHA. 1991. Air contaminants. Occupational standards permissible exposure limits. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1000.

OSHA. 2006a. Air contaminants. Occupational safety and health standards for shipyard employment. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1915.1000. http://www.osha.gov/comp-links.html. March 08, 2006.

OSHA. 2006b. Gases, vapors, fumes, dusts, and mists. Safety and health regulations for construction. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1926.55, Appendix A. http://www.osha.gov/comp-links.html. March 08, 2006.

OSHA. 2006c. Limits for air contaminants. Occupational safety and health standards. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1000. http://www.osha.gov/comp-links.html. March 08, 2006.

*OTA. 1990. Neurotoxicity: Identifying and controlling poisons of the nervous system. Washington, DC: Office of Technology Assessment, U.S. Congress. OTA-BA-438, April 1990.

Otson R. 1987. Purgeable organics in Great Lakes raw and treated water. Intern J Environ Anal Chem 31:41-53.

Otson R, Williams DT. 1982. Headspace chromatographic determination of water pollutants. Anal Chem 54:942-946.

Otson R, Fellin P, Tran Q. 1994. VOCs in representative Canadian residences. Atmos Environ 28(22):3563-3569.

Otson R, Williams DT, Bothwell PD. 1982. Volatile organic compounds in water at thirty Canadian potable water treatment facilities. J Assoc Off Anal Chem 65:1370-1374.

Owen GM, Brozek J. 1966. Influence of age, sex and nutrition on body composition during childhood and adolescence. In: Falkner F, ed. Human development. Philadelphia, PA: WB Saunders, 222-238.

Page GW. 1981. Comparison of groundwater and surface water for patterns and levels of contamination by toxic substances. Environ Sci Technol 15(12):1475-1481.

Pankow JR, Rosen ME. 1988. Determination of volatile compounds in water by purging directly to a capillary column with whole column cryotrapping. Environ Sci Technol 22:398-405.

Pankow JF, Isabelle LM, Asher WE. 1984. Trace organic compounds in rain. I. Sampler design and analysis by adsorption/thermal desorption (ATD). Environ Sci Technol 18:310-318.

Pantelitsch M. 1933. [Experiments concerning the effect of chlorinated methane and ethane on mice--The relative sensitivity of mice and cats to poisons.] Inaugural Dissertation, Hygienischen Institute der Universitat Wurzburg, 1-13. (German)

Paolini M, Sapigni E, Mesirca R, et al. 1992. On the hepatotoxicity of 1,1,2,2-tetrachloroethane. Toxicology 73:101-115.

Parmenter DC. 1921. Tetrachloroethane poisoning and its prevention. J Ind Hyg 2:456-465.

Parraga M, West JM. 1998. Hydrocarbons. In: Viccellio P, ed. Emergency toxicology. Philadelphia, PA: Lippincott-Raven Publishers, 299-313.

Pellizzari ED. 1982. Analysis for organic vapor emissions near industrial and chemical waste disposal sites. Environ Sci Technol 16:781-785.

Pellizzari ED, Hartwell TD, Harris BSH, et al. 1982. Purgeable organic compounds in mother's milk. Bull Environ Contam Toxicol 28:322-328.

Pereira MA. 1996. Carcinogenic activity of dichloroacetic acid and trichloroacetic acid in the liver of female B6C3F1 mice. Fundam Appl Toxicol 31:192-199.

Pereira MA, Phelps JB. 1996. Promotion by dichloroacetic acid and trichloroacetic acid of N-methyl-N-nitrosourea-initiated cancer in the liver of female B6C3F1 mice. Cancer Lett 102:133-141.

*Plaa GL, Larson RE. 1965. Relative nephrotoxic properties of chlorinated methane, ethane, and ethylene derivatives in mice. Toxicol Appl Pharmacol 7:37-44.

*Plaa GL, Evans EA, Hine CH. 1958. Relative hepatotoxicity of seven halogenated hydrocarbons. J Pharmacol Exp Ther 123:224-229.

Plumb RH. 1991. The occurrence of Appendix IX organic constituents in disposal site ground water. Ground Water Monit Rev 11(2):157-164.

Pratt GC, Palmer K, Wu CY, et al. 2000. An assessment of air toxics in Minnesota. Environ Health Perspect 108(9):815-825.

Quack B, Suess E. 1999. Volatile halogenated hydrocarbons over the western Pacific between 43° and 4°N. J Geophys Res 104(D1):1663-1678.

Ramsey JC, Andersen ME. 1984. A physiologically based description of the inhalation pharmacokinetics of styrene in rats and humans. Toxicol Appl Pharmacol 73:159-175.

Redmond MS, Crocker PA, McKenna KM, et al. 1996. Sediment toxicity testing with the amphipod *Ampelisca abdita* in Calcasieu Estuary, Louisiana. Arch Environ Contam Toxicol 30:53-61.

Richmond RE, Carter JH, Carter HW, et al. 1995. Immunohistochemical analysis of dichloroacetic acid (DCA)-induced hepatocarcinogenesis in male Fischer (F344) rats. Cancer Lett 92:67-76.

Roldan-Arjona T, Garcia-Pedrajas MD, Luque-Romero FL, et al. 1991. An association between mutagenicity of the Ara test of Salmonella typhimurium and carcinogenicity in rodents for 16 halogenated aliphatic hydrocarbons. Mutagenesis 6:199-205.

Rosenkranz HS. 1977. Mutagenicity of halogenated alkanes and their derivatives. Environ Health Perspect 21:79-84.

Rossberg M, Aktiengesellschaft H, Lendle W, et al. 2005. Chlorinated hydrocarbons. In: Ullman's encyclopedia of industrial chemistry. Weinheim, Germany: Wiley-VCH Verlag, 1-184.

RTECS. 2006. 1,1,2,2-Tetrachloroethane. Registry of Toxic Effects on Chemical Substances. National Institute of Occupational Safety and Health. MDL Information Systems, Inc. April 1, 2006.

Ryan DA, Argentine SM, Rice GW. 1990. Helium discharge detector for quantitation of volatile organohalogen compounds. Anal Chem 62:853-857.

Sabel GV, Clark TP. 1984. Volatile organic compounds as indicators of municipal solid waste leachate contamination. Waste Manag Res 2:119-130.

Sack TM, Steele DH, Hammerstrom K, et al. 1992. A survey of household products for volatile organic compounds. Atmos Environ 26A:1063-1070.

Sato A, Nakajima T, Koyama Y. 1980. Effects of chronic ethanol consumption on hepatic metabolism of aromatic and chlorinated hydrocarbons in rats. Br J Ind Med 37:382-386.

*Schmidt R. 1976. [The embryotoxic and teratogenic effect of tetrachloroethane experimental studies.] Biol Rundsch 14:220-223. (German)

Schmidt P, Binnevies S, Gohlke R, et al. 1972. [Subacute action of low concentration of chlorinated ethanes on rats with and without additional ethanol treatment. I. Biochemical and toxicometrical aspects, especially results in subacute and chronic toxicity studies with 1,1,2,2-tetrachloroethane.] Int Arch Arbeitsmed 30:283-298. (German)

Schmidt P, Burck D, Buerger A, et al. 1980b. [On the hepatotoxicity of benzene, 1,1,2,2-tetrachloroethane and carbon tetrachloride.] Gesamte Hyg Ihre Grenzgeb 26:167-172. (German)

Schmidt P, Gohlke R, Just A, et al. 1980a. [Combined action of hepatotoxic substances and increased environmental temperature on the liver of rats.] J Hyg Epidemiol Microbiol Immunol (Prague) 24:271-277. (German)

*Schmidt P, Ulano IP, Avilova GG, et al. 1975. [Comparison of the processes of adaptation of the organism to monotonic and intermittent exposure to 1,1,2,2-tetrachloroethane.] Gig Tr Prof Zabol 2:30-34. (Russian)

Setchell BP, Waites GMH. 1975. The blood-testis barrier. In: Creep RO, Astwood EB, Geiger SR, eds. Handbook of physiology: Endocrinology V. Washington, DC: American Physiological Society, 143-172.

Shackelford WM, Cline DM, Faas L, et al. 1983. An evaluation of automated spectrum matching for survey identification of wastewater components by gas chromatography-mass spectrometry. Anal Chim Acta 146:15-27.

Sherman JB. 1953. Eight cases of acute tetrachloroethane poisoning. J Trop Med Hyg 56:139-140.

Shilling RD. 1985. Air stripping provides fast solution for polluted well water. Pollution Engineering 17:25-27.

Shmuter LM. 1977. [The effect of chronic exposure to low concentration of ethane series chlorinated hydrocarbons on specific and nonspecific immunological reactivity in animal experiments.] Gig Tr Prof Zabol 8:38-43. (Russian)

Sieber WK, Sundin DS, Frazier TM, et al. 1991. Development use and availability of a job exposure matrix based on national occupational hazard survey data. Am J Ind Med 20:163-174.

Singh HB, Salas LJ, Smith AJ, et al. 1981. Measurements of some potentially hazardous organic chemicals in urban environments. Atmos Environ 15:601-612.

Singh HB, Salas LJ, Stiles RE. 1982. Distribution of selected gaseous mutagens and suspected carcinogens in ambient air. Environ Sci Technol 16:872-880.

Smyth HF Jr, Carpenter CP, Weil CS, et al. 1969. Range-finding toxicity data-List VII. Am Ind Hyg Assoc J 30:470-476.

Soucek P, Gut I. 1992. Cytochromes P-450 in rats: Structures, functions, properties and relevant human forms. Xenobiotica 22:83-103.

Spence JR, Hanst PL. 1978. Oxidation of chlorinated ethanes. JAPCA 28:250-253.

Spicer CW, Buxton BE, Holdren MW, et al. 1996. Variability of hazardous air pollutants in an urban area. Atmos Environ 30(20):3443-3456.

SRI. 1988. 1,1,2,2-Tetrachloroethane. Guide to chemical producers. Stanford Research Institute. Menlo Park, CA: SRI International, 123, 124, 1017.

SRI. 1992. 1,1,2,2-Tetrachloroethane. 1992 Directory of chemical producers. Stanford Research Institute. Menlo Park, CA: SRI International, 412, 1016.

SRI. 1993. 1,1,2,2-Tetrachloroethane. 1993 Directory of chemical producers. Stanford Research Institute. Menlo Park, CA: SRI International, 411.

Story DL, Meierhenry EF, Tyson CA, et al. 1986. Difference in rat liver enzyme-altered foci produced by chlorinated aliphatics and phenobarbital. Toxicol Ind Health 2:351-362.

Streete PJ, Ruprah M, Ramsey JD, et al. 1992. Detection and identification of volatile substances by headspace capillary gas chromatography to aid the diagnosis of acute poisoning. Analyst 117:1111-1127.

Strobel K, Grummt T. 1987. Aliphatic and aromatic halocarbons as potential mutagens in drinking water. III. Halogenated ethanes and ethenes. Toxicol Environ Chem 15:101-128.

Swann RL, Laskowski DA, McCall PJ, et al. 1983. A rapid method for the estimation of the environmental parameters octanol, water partition coefficient, soil sorption constant, water to air ratio, and water solubility. Res Rev 85:17-28.

Tabak HH, Quave SA, Mashni CI, et al. 1981. Biodegradability studies with organic priority pollutant compounds. J Water Pollut Contr Fed 53:1503-1518.

*Takeuchi Y. 1966. Experimental studies on the toxicity of 1,1,1,2-tetrachloroethane compared with 1,1,2,2-tetrachloroethane and 1,1,1-trichloroethane. Jpn J Ind Health 8:371-375.

Tam BN, Neumann CA. 2004. A human health assessment of hazardous air pollutants in Portland, OR. J Environ Manage 73(2):131-145.

*Theiss JC, Stoner GD, Shimkin MB, et al. 1977. Test for carcinogenicity of organic contaminants of United States drinking waters by pulmonary tumor response in strain A mice. Cancer Res 37/8:2717-2720.

Thomas RG. 1990. Volatilization from water. In: Lyman WJ, Reehl WF, Rosenblatt DH, eds. Handbook of chemical property estimation methods. New York, NY: McGraw-Hill Book Co., 15-9 to 15-30.

Thomas K, Colborn T. 1992. Organochlorine endocrine disruptors in human tissue. In: Colborn T, Clement C, eds. Chemically induced alterations in sexual and functional development: The wildlife/human connection. Princeton, NJ: Princeton Scientific Publishing, 365-394.

Tomasi A, Albano E, Bini A, et al. 1984. Free radical intermediates under hypoxic conditions in the metabolism of halogenated carcinogens. Toxicol Pathol 12:240-246.

TOMES. 1993. Toxicology, Occupational Medicine and Environment Series, electronic data base. Tetrachloroethane. Micromedex, Inc. Vol. 78. http://www.micromedex.com/products/tomes/. August 1, 2006.

Tomkins BA, Caton JE, Edwards MD, et al. 1989. Determination of regulatory organic compounds in radioactive waste samples. Volatile organics in aqueous liquids. Anal Chem 61:2751-2756.

Tomokuni K. 1969. Studies on hepatotoxicity induced by chlorinated hydrocarbons. Lipid and ATP metabolisms in the liver of mice exposed to 1,1,2,2-tetrachloroethane. Acta Med Okayama 23:273-282.

Tomokuni K. 1970. Hepatotoxicity induced by chlorinated hydrocarbons. II. Lipid metabolism and absorption spectrum of microsomal lipids in the mice exposed to 1,1,2,2-tetrachloroethane. Acta Med Okayama 24:315-322.

Tosato ML, Chiorboli C, Eriksson L, et al. 1991. Multivariate modeling of the rate constant of the gas-phase reaction of haloalkanes with the hydroxyl radical. Sci Total Environ 109/110:307-325.

Travis CC, Holton GA, Etnier EL, et al. 1986. Assessment of inhalation and ingestion population exposures from incinerated hazardous wastes. Environ Int 12:533-540.

TRI05. 2007. TRI exporer: Providing access to EPA's toxics release inventory data. Washington, DC: Office of Information Analysis and Access. Office of Environmental Information. U.S. Environmental Protection Agency. Toxics Release Inventory. http://www.epa.gov/triexplorer/. December 21, 2007.

Truffert L, Girard-Wallon C, Emmerich E, et al. 1977. [Early experimental demonstration of the hepatotoxicity of some chlorinated solvents by the study of the synthesis of hepatic DNA.] Arch Mal Prof Med Trav Secur Soc 38:261-263. (French)

Tsuruta H. 1975. Comparative study in the in vivo percutaneous absorptions of chlorinated solvents in mice. Ind Health 13:227-236

Tu AS, Murray TA, Hatch KM, et al. 1985. In vitro transformation of BALB/c-3T3 cells by chlorinated ethanes and ethylenes. Cancer Lett 28:85-92.

Union Carbide Corporation. 1947. Repeated exposure of rats and dogs to vapors of eight chlorinated hydrocarbons. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0515559.

U.S. Department of Commerce. 2006. 2903191000--Hexachloroethane and tetrachloroethane. U.S. Department of Commerce. Office of Trade and Industry Information (OTII), International Trade Administration. http://www.ita.doc.gov/td/industry/otea/Trade-Detail/. March 30, 2006.

USGS. 1983. Total recoverable purgeable organic compounds in water by purge and trap gas chromatography with a mass spectrometer. In: Methods for the determination of organic substances in water and fluvial sediments, techniques of water-resources investigations of the United States Geological Survey. Denver, CO: U.S. Geological Survey. http://web1.er.usgs.gov/nemi/method_summary.jsp?param_method_id=4772. June 5, 2006.

USGS. 1998. Methods of analysis by the U.S. Geological Survey National Water Quality Laboratory: Determination of 86 volatile organic compounds in water by gas chromatography/mass spectrometry, including detections less than reporting limits. Denver, CO: U.S. Geological Survey. Open File Report 97-829.

USGS. 2001. Ground-water quality in the Cook Inlet Basin, Alaska, 1999. Anchorage, AK: U.S. Geological Survey, U.S. Department of the Interior. WRI Report No. 01-4208.

USGS. 2002. Quality of shallow ground water in areas of recent residential and commercial development, Wichita, Kansas, 2000. U S Geological Survey- U S Department of the Interior. Water Resources Investigation Report 02-4228. http://ks.water.usgs.gov/Kansas/pubs/reports/wrir.02-4228.pdf. December 26, 2007.

USITC. 1994. Harmonized tariff schedule of the United States 1994. Washington, DC: U.S. International Trade Commission Publication 2690.

*Vainio H, Parkki MG, Marniemi J. 1976. Effects of aliphatic chlorohydrocarbons on drug-metabolizing enzymes in rat liver in vivo. Xenobiotica 6(10):599-604.

Valsaraj KT, Kommalapati RR, Robertson ED, et al. 1999. Partition constants and adsorption/desorption hysteresis for volatile organic compounds on soil from a Louisiana superfund site. Environ Monit Assess 58:225-241.

*Van Dyke RA, Wineman CG. 1971. Enzymatic dechlorination of chloroethanes and propanes in vitro. Biochem Pharmacol 20:463-470.

Verschueren K. 2001. Handbook of environmental data on organic chemicals. 4th ed. New York, NY: John Wiley & Sons, Inc., 1946-1947.

Vieira I, Sonnier M, Cresteil T. 1996. Developmental expression of CYP2E1 in the human liver: Hypermethylation control of gene expression during the neonatal period. Eur J Biochem 238:476-483.

Vogel EW, Nivard MJM. 1993. Performance of 181 chemicals in a Drosophila assay predominantly monitoring interchromosomal mitotic recombination. Mutagenesis 8:57-81.

Ward JM. 1955. Accidental poisoning with tetrachloroethane. Br Med J 1:1136.

Warner JR, Hughes TJ, Claxton LD. 1988. Evaluation of a protocol for preparing soil and sediment samples for AMES mutagenicity testing. Environ Mol Mutagen 11:111.

West JR, Smith HW, Chasis H. 1948. Glomerular filtration rate, effective renal blood flow, and maximal tubular excretory capacity in infancy. J Pediatr 32:10-18.

Westrick JJ, Mello JW, Thomas RF. 1984. The groundwater supply survey. J Am Water Works Assoc 76:52-59.

WHO. 1998. 1,1,2,2-Tetrachloroethane. Concise international chemical assessment document no. 3. International programme on chemical safety. Geneva, Switzerland: World Health Organization. http://www.inchem.org/documents/cicads/cicads/cicad03.htm. April 07, 2006.

WHO. 2000. Air quality guidelines. 2nd ed. Geneva, Switzerland: World Health Organization. http://www.euro.who.int/Document/AIQ/AirQualRepMtg.pdf. March 08, 2006.

WHO. 2004. Guidelines for drinking-water quality. 3rd ed. Geneva, Switzerland: World Health Organization. http://www.who.int/water_sanitation_health/dwq/gdwq3/en/. March 08, 2006.

Widdowson EM, Dickerson JWT. 1964. Chemical composition of the body. In: Comar CL, Bronner F, eds. Mineral metabolism: An advanced treatise. Volume II: The elements Part A. New York: Academic Press, 1-247.

Willcox WH, Spilsbury BH, Legge TM. 1915. An outbreak of toxic jaundice of a new type amongst aeroplane workers-Its clinical and toxicological aspect. Trans Med Soc London 38:129-156.

Wilson SC, Burnette V, Waterhouse KS, et al. 1994. Volatile organic compounds in digested United Kingdom sewage sludges. Environ Sci Technol 28(2):259-266.

*Wolff DL, Siegmund R. 1978. [The circadian-dependent effect of trichloroethylene on spontaneous locomotor activity and of tetrachloroethane on mortality in mice.] Biol Zentralbl 97(3):345-351. (German)

Wolff L. 1978. The effect of 1,1,2,2-tetrachloroethane on passive avoidance learning and spontaneous locomotor activity. Activ Nerv Sup (Praha) 20:14-16.

Woodruff RC, Mason JM, Valencia R, et al. 1985. Chemical mutagenesis testing in drosophila. 5. Results of 53 coded compounds tested for the National Toxicology Program. Environ Mutagen 7:677-702.

Yasuda SK, Loughran ED. 1977. Air sampling methods for S-tetrachloroethane and other related chlorinated hydrocarbons. J Chromatogr 137:283-292.

Yieru H, Qing-Yu O, Weile Y. 1990a. The effect of compound structure on the elemental responses in gas chromatography - microwave induced plasma atomic emission spectrometry. J Chromatogr Sci 28:584-588.

Yieru H, Qing-Yu O, Weile Y. 1990b. Characteristics of flame ionization detection for the quantitative analysis of complex organic mixtures. Anal Chem 62:2063-2064.

Yllner S. 1971. Metabolism of 1,1,2,2-tetrachloroethane-14C in the mouse. Acta Pharmacol Toxicol 29:499-512.

Ziegler EE, Edwards BB, Jensen RL, et al. 1978. Absorption and retention of lead by infants. Pediatr Res 12:29-34.

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10. GLOSSARY

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD)—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

Cancer Effect Level (CEL)—The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure—Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs—Substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (EPA) Health Advisory—An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

Immediately Dangerous to Life or Health (IDLH)—The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

Immunological Effects—Functional changes in the immune response.

Incidence—The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An OR of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Organophosphate or Organophosphorus Compound—A phosphorus-containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q_1*—The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µg/L for water, mg/kg/day for food, and µg/m^3 for air).

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL, from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 minutes continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily Threshold Limit Value-Time Weighted Average (TLV-TWA) may not be exceeded.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

Time-Weighted Average (TWA)—An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose$_{(50)}$ (TD$_{50}$)—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic—The absorption, distribution, and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis, 3 being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any chemical that is foreign to the biological system.

10. GLOSSARY

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APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

APPENDIX A

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Environmental Medicine, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Environmental Medicine, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,1,2,2-Tetrachloroethane
CAS Numbers: 79-34-5
Date: June 2008
Profile Status: Post-Public Third Draft
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 39
Species: Rat

Minimal Risk Level: [0.5] mg/kg/day [ ] ppm

Reference: NTP. 2004a. NTP technical report on the toxicity studies of 1,1,2,2-tetrachloroethane (CAS No. 79-34-5) administered in microcapsules in feed to F433/N rats and B6C3F_1 mice. Research Triangle Park, NC: National Toxicology Program. TR-49. NIH Publication No. 04-4414.

Experimental design: Groups of 10 male and 10 female F344/N rats were fed diets containing 0, 268, 589, 1,180, 2,300, or 4,600 ppm of microencapsulated 1,1,2,2-tetrachloroethane for 14 weeks. The reported average daily doses were 0, 20, 40, 80, 170, or 320 mg/kg/day; vehicle control (feed with empty microcapsules) and untreated control groups were used for both sexes. End points evaluated throughout the study included clinical signs, body weight, and feed consumption. Hematology (12 indices) and clinical chemistry (10 indices) were assessed on days 5 and 21 and at the end of the study; urinalyses were not performed. Necropsies were performed on all animals and selected organs (liver, heart, right kidney, lung, right testis, and thymus) were weighed. Comprehensive histological examinations were performed on untreated control, vehicle control, and high dose groups. Tissues examined in the lower dose groups were limited to bone with marrow, clitoral gland, liver, ovary, prostate gland, spleen, testis with epididymis and seminal vesicle, and uterus. Functional observational batteries (FOBs) (21 parameters) were performed on rats in both control groups and the 20, 40, and 80 mg/kg/day groups during weeks 4 and 13. Sperm evaluations and vaginal cytology evaluations were performed at 0, 40, 80, and 170 mg/kg/day. The sperm evaluations consisted of spermatid heads per testis and per gram testis, spermatid counts, and epididymal spermatozoal motility and concentration. The vaginal cytology evaluations consisted of percentage of time spent in the various estrus stages and estrous cycle length.

Effects noted in study and corresponding doses: All rats survived to the end of the study, but clinical signs of thinness and pallor were observed in all animals in the 170 and 320 mg/kg/day groups. Final body weights were statistically significantly lower than vehicle controls in males at 80, 170, and 320 mg/kg/day (7, 29, and 65% lower, respectively) and females at 40, 80, 170, and 320 mg/kg/day (3, 9, 29, and 56% lower, respectively); at 320 mg/kg/day, rats of both sexes lost weight. Feed consumption decreased with increasing dose level at 170 and 320 mg/kg/day and may have contributed to the reduced body weight gain and weight loss. Results of the FOBs showed no exposure-related findings of neurotoxicity. The hematology evaluations indicated that 1,1,2,2-tetrachloroethane affected the circulating erythroid mass in both sexes (Table A-1). There was evidence of a transient erythrocytosis, as shown by increases in hematocrit values, hemoglobin concentration, and erythrocyte counts on days 5 and 21 at ≥170 mg/kg/day. The erythrocytosis was not considered clinically significant and disappeared by week 14, at which time it was replaced by minimal to mild, dose-related anemia, as shown by decreases in hematocrit and hemoglobin at ≥40 mg/kg/day. For example, although males exposed to 40 mg/kg/day showed a statistically significant decrease in hemoglobin at week 14, the magnitude of the change was small (3.8%). The anemia was characterized as microcytic based on evidence suggesting that the circulating erythrocytes were smaller than expected; this included decreases in mean cell volumes, mean cell hemoglobin values, and mean cell hemoglobin concentration in both sexes at ≥80 mg/kg/day at

various time points. At week 14, there were no changes in reticulocyte counts, suggesting that there was no erythropoietic response to the anemia; this was supported by bone marrow atrophy observed microscopically. As discussed by NTP (2004a), the erythrocytosis suggested a physiological response consistent with the hemoconcentration of dehydration, and compromised nutritional status due to the reduced weight gain and food consumption may have contributed to the development of the anemia.

Table A-1. Body Weight, Liver Weight, and Selected Serum Chemistry and Hematology Changes in Rats Exposed to 1,1,2,2-Tetrachloroethane in the Diet for 14 Weeks[a]

End point	Vehicle control	Dose (mg/kg/day)				
		20	40	80	170	320
Males (10/group)						
Body weight (g)	366±5	354±9	353±6	341±6[b]	259±9[b]	127±5[b]
Liver weight						
absolute (g)	12.74±0.26	12.99±0.35	14.47±0.44	15.54±0.39	11.60±0.44[b]	6.57±0.18[b]
relative (%)	34.79±0.42	36.72±0.44	41.03±0.85[b]	45.61±0.52[b]	44.68±0.45[b]	52.23±1.42[b]
Serum total protein (g/dL)	7.2±0.1	7.3±0.1	7.3±0.1	7.3±0.1	6.7±0.1[b]	6.0±0.1[b]
Serum cholesterol (mg/dL)	73±2	74±3	76±2	67±2	68±2	65±2[b]
ALT (IU/L)	48±2	49±2	53±2	69±3[b]	115±8[b]	292±18[b]
ALP (IU/L)	256±7	260±5	248±5	245±6	353±12[b]	432±24[b]
SDH (IU/L)	23±1	27±1[b]	26±2	31±1[b]	47±2[b]	74±4[b]
Bile acids (µmol/L)	29.2±2.9	27.5±2.7	27.2±2.7	35.9±3.9	92.0±16.6[b]	332.4±47.4[b]
Hematocrit (%) (automated)	45.2±0.5	44.9±0.4	44.0±0.9	43.3±0.7	43.1±0.6[b]	39.0±1.1[b]
Hemoglobin (Hb) (g/dL)	15.8±0.1	15.6±0.1	15.2±0.3[b]	14.9±0.1[b]	14.6±0.1[b]	13.6±0.3[b]
Mean cell volume (fL)	50.7±0.1	51.8±0.3	52.3±0.2	51.3±0.2	49.4±0.2	44.4±0.4[b]
Mean cell Hb (pg)	17.7±0.1	18.1±0.1	18.0±0.1	17.7±0.2	16.8±0.1[b]	15.5±0.2[b]
Platelets (10^3/µL)	728.4±12.3	707.0±5.8	727.0±25.2	716.3±9.7	692.8±12.6[b]	773.4±23.2[b]

Table A-1. Body Weight, Liver Weight, and Selected Serum Chemistry and Hematology Changes in Rats Exposed to 1,1,2,2-Tetrachloroethane in the Diet for 14 Weeks[a]

End point	Vehicle control	Dose (mg/kg/day)				
		20	40	80	170	320
Females (10/group)						
Body weight (g)	195±4	192±4	189±2	177±2[b]	139±4[b]	85±3[b]
Liver weight						
absolute (g)	6.84±0.17	7.03±0.12	7.14±0.16	7.80±0.08[b]	6.66±0.21	4.94±0.12[b]
relative (%)	35.07±0.56	36.69±0.36	37.84±0.51[b]	44.20±0.27[b]	48.03±0.89[b]	58.40±1.42[b]
Serum total protein (g/dL)	7.2±0.1	7.3±0.0	7.3±0.1	6.9±0.1	6.4±0.1[b]	5.6±0.1[b]
Serum cholesterol (mg/dL)	104±4	105±3	98±1	81±2[b]	64±3[b]	55±3[b]
ALT (IU/L)	46±2	42±1	41±2	49±2	112±7[b]	339±18[b]
ALP (IU/L)	227±5	216±4	220±3	225±11	341±7[b]	468±22[b]
SDH (IU/L)	27±1	27±1	28±2	25±1	45±3[b]	82±3[b]
Bile acids (µmol/L)	37.0±7.1	46.6±6.5	39.1±5.6	36.3±3.9	39.3±7.9	321.5±50.6[b]
Hematocrit (%) (automated)	42.8±0.4	43.2±0.4	42.1±0.4	40.1±0.5[b]	42.8±0.7	34.7±0.7[b]
Hb (g/dL)	15.2±0.1	15.3±0.1	14.9±0.1	14.2±0.2[b]	14.5±0.2[b]	12.5±0.2[b]
Mean cell volume (fL)	55.4±0.1	56.1±0.1	55.8±0.1	53.3±0.2[b]	49.0±0.2[b]	44.4±0.4[b]
Mean cell Hb (pg)	19.7±0.1	19.8±0.1	19.7±0.1	18.9±0.1[b]	16.6±0.2[b]	16.0±0.2[b]
Platelets (10^3/µL)	742.1±20.4	725.9±12.7	733.9±8.8	727.4±14.2	639.4±9.9[b]	662.5±19.4[b]

[a]Mean±standard error.
[b]Significantly different (p≤0.05) from control value by William's test (body and liver weight data) or Dunn's or Shirley's test (clinical chemistry and hematology data).

ALP = alkaline phosphatase; ALT = alanine aminotransferase; SDH = sorbitol dehydrogenase

Source: NTP 2004a

Statistically significant increases in absolute and relative liver weights were observed in males and females exposed to ≥40 mg/kg/day (Table A-1). Significant alterations in absolute and/or relative weights were also observed in several other organs, but these changes likely reflected the decreased body weight gain associated with reduced food intake. Changes in serum clinical chemistry parameters indicative of liver damage were observed in both sexes, generally occurring at all time points (day 5, day 21, and week 14) and generally increasing in magnitude with increasing dose and time. At week 14 (Table A-1), these effects included statistically significant increases in ALT and SDH in males at ≥80 mg/kg/day and females at ≥170 mg/kg/day, increases in ALP in both sexes at ≥170 mg/kg/day, increases in bile acids in males at ≥170 mg/kg/day and females at 320 mg/kg/day, and decreases in serum cholesterol in females at ≥80 mg/kg/day and males at 320 mg/kg/day. There were no exposure-related changes in serum 5'-nucleotidase at week 14, although increases occurred on day 5 in females at ≥20 mg/kg/day and on day 21 in males and females at 80, 170, and/or 320 mg/kg/day. As discussed by NTP (2004a), increases in ALT and SDH are specific markers of hepatocellular necrosis or increased cell membrane permeability (leakage) in rodents; increases in bile acids are markers of cholestasis, impaired

hepatocellular function, or hepatocellular injury; increases in ALP and 5'-nucleotidase are other markers of cholestasis; and decreases in serum cholesterol could be indicative of liver dysfunction (impaired cholesterol biosynthesis). The LOAEL for serum chemistry effects is 170 mg/kg/day because the magnitude of the changes in serum ALT, SDH, and cholesterol at 80 mg/kg/day were less than 2-fold different from controls and not considered to be biologically significant.

Histological evaluation presented further evidence of the liver as the primary target of 1,1,2,2-tetrachloroethane toxicity; a summary of histological changes is presented in Table A-2. Hepatic cytoplasmic vacuolization was noted in males exposed to 20 mg/kg/day or more and females exposed to 40 mg/kg/day or more. Although the incidence of this alteration was high in affected groups, severity was only minimal-to-mild and did not increase with dose. Females exposed to 80 mg/kg/day showed an increase in the incidence of hepatocyte hypertrophy, which increased in severity and incidence with increasing exposure level; similar results were seen in males, but were not statistically significant below 170 mg/kg/day. At ≥170 mg/kg/day, additional effects in the liver in both sexes were hepatocyte necrosis, pigmentation, mitotic alteration and mixed cell foci, and bile duct hyperplasia. Pigmentation of the spleen was increased in male rats exposed to ≥80 mg/kg/day and in female rats exposed to ≥170 mg/kg/day. Other histological effects included high incidences (70–100%) of atrophy in the spleen (red pulp and lymphoid follicle) of both sexes at 320 mg/kg/day, bone (metaphysis) and bone marrow in females at ≥170 mg/kg/day and males at 320 mg/kg/day, and male and female reproductive tissues at 320 mg/kg/day. The reductions in body weight gain at 170 mg/kg/day and body weight losses at 320 mg/kg/day may have contributed to the atrophy of the bone, bone marrow, and reproductive tissues.

Table A-2. Incidences of Selected Histopathological Lesions in Rats Exposed to 1,1,2,2-Tetrachloroethane in the Diet for 14 Weeks

	Vehicle	Dose (mg/kg/day)				
End point	control	20	40	80	170	320
Males (10/group)[a]						
Hepatocyte cytoplasmic vacuolization	0	7[b] (1.3)	9[b] (2.0)	10[b] (1.9)	8[b] (1.4)	0
Hepatocyte hypertrophy	0	0	0	1 (1.0)	9[b] (1.3)	10[b] (3.2)
Hepatocyte necrosis	0	0	0	0	8[b] (1.0)	10[b] (1.6)
Hepatocyte pigmentation	0	0	0	0	7[b] (1.0)	10[b] (1.9)
Hepatocyte mitotic alteration	0	0	0	0	0	6[b] (2.0)
Mixed cell foci	0	0	0	0	3	5[b]
Bile duct hyperplasia	0	0	0	0	0	10[b] (1.7)
Spleen pigmentation	0	0	1 (1.0)	9[b] (1.0)	9[b] (1.0)	9[b] (1.6)
Spleen red pulp atrophy	0	0	0	0	5[b] (1.0)	9[b] (1.4)
Spleen lymphoid follicle atrophy	0	0	0	0	0	5[b] (1.0)

Table A-2. Incidences of Selected Histopathological Lesions in Rats Exposed to 1,1,2,2-Tetrachloroethane in the Diet for 14 Weeks

End point	Vehicle control	Dose (mg/kg/day) 20	40	80	170	320
Females (10/group)[a]						
Hepatocyte cytoplasmic vacuolization	0	0	10[b] (1.7)	10[b] (2.2)	4[b] (1.3)	0
Hepatocyte hypertrophy	0	0	0	4[b] (1.0)	10[b] (1.7)	10[b] (2.8)
Hepatocyte necrosis	0	0	0	1 (1.0)	7[b] (1.0)	10[b] (1.1)
Hepatocyte pigmentation	0	0	0	0	10[b] (1.3)	10[b] (2.0)
Hepatocyte mitotic alteration	0	0	0	0	3 (2.0)	10[b] (1.9)
Mixed cell foci	0	0	0	0	8[b]	1
Bile duct hyperplasia	0	0	0	0	5[b] (1.0)	10[b] (1.9)
Spleen pigmentation	1 (1.0)	0	0	4 (1.0)	8[b] (1.1)	8[b] (1.3)
Spleen, red pulp atrophy	0	0	0	0	0	9[b] (1.6)
Spleen lymphoid follicle atrophy	0	0	0	0	0	3 (1.0)

[a]Values represent number of animals with the lesion, with the severity score in parenthesis; severity grades are as follows: 1=minimal, 2=mild, 3=moderate, 4=severe.
[b]Significantly different ($p \leq 0.01$) from vehicle control group by the Fisher Exact Test.

Source: NTP 2004a

Reproductive effects in the males included statistically significant reductions in sperm motility at ≥40 mg/kg/day (18–22% less than vehicle controls), reductions in absolute epididymis weight at ≥80 mg/kg/day and absolute left cauda epididymis weight at 170 mg/kg/day (relative organ weights not reported), and increases in incidences (90–100%) of minimal to moderate atrophy of the prostate gland, seminal vesicle, and testicular germinal epithelium at 320 mg/kg/day. Reproductive effects in the females included statistically significant increases in incidences (70–100%) of minimal to mild uterine atrophy at ≥170 mg/kg/day, clitoral gland atrophy at 320 mg/kg/day, and ovarian interstitial cell cytoplasmic alterations at 320 mg/kg/day. The vaginal cytology evaluations indicated that the females in the 170 mg/kg/day group (320 mg/kg/day not evaluated) spent more time in diestrus and less time in proestrus, estrus, and metestrus than did the vehicle controls. The body weight loss at 320 mg/kg/day and reduced body weight gain at the lower dose levels could have contributed to the atrophy and other effects in both sexes. The LOAEL for male rat reproductive effects is 320 mg/kg/day based on atrophy in the prostate gland, seminal vesicle, and testicular germinal epithelium. The effects in males at lower doses are not judged to be adverse, indicating that the male reproductive NOAEL is 170 mg/kg/day. In particular, the male reproductive organ weight decreases at 80 and 170 mg/kg/day are not considered adverse due to a lack of accompanying histopathology. The reductions in sperm motility at ≥40 mg/kg/day are not considered adverse because the decreases are small, not dose-related, not accompanied by decreased sperm counts, and of unclear reproductive significance. The LOAEL for female rat reproductive effects is 170 mg/kg/day based on uterine atrophy and estrus cycle alterations; the corresponding NOAEL is 80 mg/kg/day.

In summary, this study provides evidence that the liver was the primary target of 1,1,2,2-tetrachloroethane toxicity in rats. At the lowest dose tested, 20 mg/kg/day, there was a significant increase in the incidence of hepatic cytoplasmic vacuolization in males; this minimal effect, which did not increase in severity with

dose, was not considered adverse by NTP (2004a). At 40 mg/kg/day, significant increases in relative liver weights were observed. Hepatocellular hypertrophy, spleen pigmentation, and decreases in body weight gain (<10%) were observed at 80 mg/kg/day, although these changes were generally of minimal severity or adaptive in nature. Increases in serum ALT and SDH and decreases in serum cholesterol also occurred at ≥80 mg/kg/day, but the magnitudes of these changes were biologically significant only at ≥170 mg/kg/day. Other effects that occurred at 170 and 320 mg/kg/day included increases in serum ALP and bile acids, hepatocyte necrosis, bile duct hyperplasia, hepatocellular mitotic alterations, foci of cellular alterations, and liver pigmentation. This study identified a NOAEL of 80 mg/kg/day and a LOAEL of 170 mg/kg/day for systemic toxicity based on adverse liver-related serum chemistry changes and histological manifestations of hepatocellular damage. This LOAEL is lower than or equal to the LOAELs for reproductive effects in males (320 mg/kg/day) and females (170 mg/kg/day). A LOAEL for neurotoxicity was not identified because there were no clinical signs of neurotoxicity or exposure-related findings in the FOB at doses as high as 80 mg/kg/day (highest tested dose in the FOB). These findings suggest that the nervous system is less sensitive than the liver for intermediate-duration dietary exposure.

Dose and end point used for MRL derivation:

[ ] NOAEL [ ] LOAEL [X] BMDL

Based on benchmark dose analysis of dose-response data for various liver effects, a $BMDL_{10}$ of 53.88 mg/kg/day for hepatocyte necrosis was selected as the point of departure for the MRL. The BMD analysis and basis for selection of the point of departure are presented in the last section of this worksheet.

Uncertainty Factors used in MRL derivation:

[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Average daily doses were reported by the investigators.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable (*ad libitum* dietary exposure).

Other additional studies or pertinent information that lend support to this MRL: The NTP (2004a) study also tested mice that were exposed to 1,1,2,2-tetrachloroethane in the diet for 14 weeks. As detailed below, this study found that the mice were less sensitive than the rats, as reflected by the liver toxicity findings, which identified LOAELs and NOAELs that were higher in the mice (300 and 200 mg/kg/day) than in the rats (170 and 80 mg/kg/day). Groups of 10 male and 10 female B6C3F1 mice were exposed to diets containing 0, 589, 1,120, 2,300, 4,550, or 9,100 ppm of microencapsulated 1,1,2,2-tetrachloroethane for 14 weeks. The reported average daily doses were 0, 100, 200, 370, 700, or 1,360 mg/kg/day for males and 80, 160, 300, 600, or 1,400 mg/kg/day for females; vehicle and untreated control groups were used for each sex. End points evaluated throughout the study included clinical signs, body weight, and feed consumption. Clinical chemistry (10 indices) was assessed at the end of the study; hematology evaluations and urinalyses were not performed. Necropsies were conducted on all animals and selected organs (liver, heart, right kidney, lung, right testis, and thymus) were weighed. Comprehensive histological examinations were performed on untreated control, vehicle control, and high dose groups. Tissues examined in the lower dose groups were limited to the liver, spleen, and thymus in both sexes,

preputial gland in males, and lungs in females. FOBs (21 parameters) were performed on mice in both control and 160/200, 300/370, and 600/700 mg/kg/day groups during weeks 4 and 13. Sperm motility, vaginal cytology, estrous cycle length, and percentage of time spent in the various estrus stages were evaluated in both control and 160/200, 600/700, and 1,360/1,400 mg/kg/day groups.

All mice survived to the end of the study. A clinical sign of thinness was observed at 300/370 mg/kg/day (3/10 males, 1/10 females), 600/700 mg/kg/day (9/10 males, 2/10 females), and 1,360/1,400 mg/kg/day (10/10 males, 10/10 females). Final body weights were significantly lower than vehicle controls in male mice at 370, 700, and 1,360 mg/kg/day (12, 16, and 33% reduced, respectively) and female mice at 300, 600, and 1,400 mg/kg/day (4, 10, and 11% reduced, respectively) (Table A-3). Feed consumption was slightly less than controls in males at ≥700 mg/kg/day, but similar to controls in females. Significant increases in absolute and relative liver weights were observed in the male mice exposed to 200 mg/kg/day or higher and in female mice exposed to 80 mg/kg/day or higher (Table A-3). Other organ weight changes (increased kidney weights in males at ≥370 mg/kg/day and increased thymus weights in both sexes at 1,360/1,400 mg/kg/day) were considered to be secondary to the body weight changes. Results of the FOBs showed no exposure-related neurotoxicity.

Table A-3. Body Weight, Liver Weight, and Selected Clinical Chemistry Changes in Mice Exposed to Microencapsulated 1,1,2,2-Tetrachloroethane in the Diet for 14 Weeks[a]

	Vehicle	Dose (mg/kg/day)				
End point	control	100	200	370	700	1,360
Males (10/group)						
Body weight (g)	30.1±0.6	30.6±0.6	30.0±0.3	26.5±0.4[b]	25.2±0.2[b]	23.1±0.5[b]
Liver weight						
absolute (g)	1.47±0.02	1.56±0.04	1.70±0.02[b]	1.61±0.04[b]	1.53±0.05	1.56±0.04
relative (%)	48.84±1.17	50.94±0.93	56.82±0.63[b]	60.63±1.20[b]	60.71±1.76[b]	67.43±1.83[b]
Serum total protein (g/dL)	5.4±0.1	5.2±0.1	5.1±0.1[b]	5.1±0.1[b]	5.1±0.1[b]	5.1±0.1[b]
Serum cholesterol (mg/dL)	131±7	125±4	94±3[b]	110±5	112±4	126±5
ALT (IU/L)	66±8	62±19	74±8	207±18[b]	172±18[b]	296±24[b]
ALP (IU/L)	85±2	78±2	89±2	130±3[b]	143±7[b]	184±11[b]
SDH (IU/L)	55±3	53±2	76±3[b]	288±20[b]	288±29[b]	448±25[b]
5'-Nucleo-tidase (IU/L)	18±1	16±1	18±0	30±2[b]	37±3[b]	62±7[b]
Bile acids (µmol/L)	25.3±1.2	22.8±1.5	24.8±0.6	56.5±5.1[b]	63.3±7.5[b]	108.7±8.1[b]

Table A-3. Body Weight, Liver Weight, and Selected Clinical Chemistry Changes in Mice Exposed to Microencapsulated 1,1,2,2-Tetrachloroethane in the Diet for 14 Weeks[a]

End point	Vehicle control	Dose (mg/kg/day)				
		80	160	300	600	1,400
Females (10/group)						
Body weight (g)	24.3±0.5	24.2±0.2	24.3±0.6	23.3±0.4	21.7±0.2[b]	21.5±0.6[b]
Liver weight						
absolute (g)	1.05±0.03	1.16±0.02[b]	1.36±0.06[b]	1.34±0.04[b]	1.28±0.03[b]	1.39±0.05[b]
relative (%)	43.26±1.05	47.90±0.85[b]	55.54±1.17[b]	57.39±0.84[b]	58.73±1.23[b]	64.42±1.14[b]
Serum total protein (g/dL)	5.6±0.1	5.6±0.1	5.5±0.0	5.4±0.1[b]	5.4±0.0[b]	5.1±0.1[b]
Serum cholesterol (mg/dL)	109±2	109±3	85±3[b]	68±2[b]	64±3[b]	92±4[b]
ALT (IU/L)	34±5	50±15	65±5[b]	189±33[b]	197±21[b]	351±35[b]
ALP (IU/L)	131±5	126±2	139±5	150±3[b]	161±7[b]	195±6[b]
SDH (IU/L)	36±1	44±3[b]	76±4[b]	197±15[b]	243±23[b]	461±59[b]
5'-Nucleo-tidase (IU/L)	59±3	71±2	84±5[b]	62±2	62±3	83±4[b]
Bile acids (µmol/L)	27.2±1.2	26.1±1.9	30.9±1.1[b]	44.2±3.9[b]	51.5±3.6[b]	101.7±12.0[b]

[a]Mean±standard error.
[b]Statistically significantly different from control value.

ALP = alkaline phosphatase; ALT = alanine aminotransferase; SDH = sorbitol dehydrogenase

Source: NTP 2004a

Clinical chemistry findings in the mice are summarized in Table A-3 and included statistically significant decreases in serum total protein in males at ≥200 mg/kg/day, serum total protein in females at ≥300 mg/kg/day, and serum albumin in females at 1,400 mg/kg/day. Decreased serum albumin could not fully account for the decreased total protein concentrations, suggesting that other factors (e.g., changes in other protein fractions, hydration status, and/or hepatic function) contributed to the hypoproteinemia (NTP 2004a). Other serum chemistry changes were indicative of dose-related liver effects beginning at 160 mg/kg/day; these included statistically significant increased SDH in both sexes at ≥160/200 mg/kg/day, decreased serum cholesterol in females at ≥160 mg/kg/day, increased ALT and total bile acids in females at ≥160 and males at ≥370 mg/kg/day, increased ALP in both sexes at 300/370 mg/kg/day, and increased 5'-nucleotidase in males at ≥370 mg/kg/day. As previously discussed for the rat study, these serum indices are markers of hepatocellular damage, cholestasis, and/or impaired hepatic function (NTP 2004a). The magnitudes of the serum chemistry changes were biologically significant (e.g., greater than 2-fold increases in serum ALT and SDH) at ≥300 mg/kg/day in females and ≥370 mg/kg/day in males.

Histopathological findings are consistent with the serum chemistry data in indicating that the liver is the most sensitive target of 1,1,2,2-tetrachloroethane toxicity in the mice. As summarized in Table A-4,

minimal hepatocyte hypertrophy was observed at ≥160 mg/kg/day in females and ≥200 mg/kg/day in males. This effect is likely to be an adaptive non-adverse hepatic response. Degenerative and other adverse liver lesions, including necrosis, pigmentation, and bile duct hyperplasia, occurred at ≥300 mg/kg/day in females and ≥370 mg/kg/day in males. Other histological findings included increased incidences of preputial gland atrophy in the 100, 700, and 1,360 mg/kg/day male groups (Table A-4), but this effect was not clearly dose-related and is possibly associated with decreased body weight gain. Based on the adverse serum chemistry and histopathological changes at 300 mg/kg/day and higher doses, this study identifies a LOAEL of 300 mg/kg/day for liver toxicity in mice; the corresponding NOAEL is 200 mg/kg/day.

Table A-4. Incidences of Selected Histopathological Lesions in Mice Exposed to Microencapsulated 1,1,2,2-Tetrachloroethane in the Diet for 14 Weeks

	Vehicle	Dose (mg/kg/day)				
End point	control	100	200	370	700	1,360
Males (10/group)[a]						
Hepatocyte hypertrophy	0	0	7[b] (1.0)	10[b] (2.2)	10[b] (2.8)	10[b] (3.1)
Hepatocyte necrosis	0	0	1 (2.0)	8[b] (1.1)	8[b] (1.0)	9[b] (1.0)
Liver focal pigmentation	0	0	0	10[b] (1.2)	10[b] (1.4)	8[b] (1.3)
Bile duct hyperplasia	0	0	0	7[b] (1.4)	9[b] (1.3)	10[b] (2.0)
Preputial gland atrophy	0	4[b] (2.0)	2 (1.0)	0	4[b] (2.5)	5[b] (2.2)

	Vehicle	Dose (mg/kg/day)				
End point	control	80	160	300	600	1,400
Females (10/group)[a]						
Hepatocyte hypertrophy	0	2 (1.5)	9[b] (1.0)	10[b] (1.9)	10[b] (2.5)	10[b] (3.0)
Hepatocyte necrosis	0	0	0	3 (1.0)	7[b] (1.0)	4[b] (1.0)
Liver focal pigmentation	0	0	2 (1.0)	9[b] (1.0)	8[b] (1.0)	7[b] (1.1)
Bile duct hyperplasia	0	0	0	8[b] (1.0)	10[b] (1.4)	10[b] (2.0)

[a]Values represent number of animals with the lesion, with the severity score in parenthesis; severity grades are as follows: 1=minimal, 2=mild, 3=moderate, 4=severe.
[b]Significantly different from vehicle control group.

Source: NTP 2004a

Additional information on the intermediate-duration oral toxicity of 1,1,2,2-tetrachloroethane is available from a 21-day gavage study in rats (NTP 1996), a 16-day gavage study in mice (NTP 1993d), 6-week gavage studies in rats and mice (NCI 1978), and 15-day diet studies in rats and mice (NTP 2004a). These studies are mainly dose range-finding studies that used small numbers of animals and had limited or no evaluations of clinical chemistry and histology. Key findings include reduced body weight gain in rats exposed to 100 mg/kg/day by gavage for 6 weeks (NCI 1978) or 300 mg/kg/day in the diet for 15 days (NTP 2004a), cytoplasmic vacuolation in the liver at 104 mg/kg/day and clinical signs of neurotoxicity and mortality at 208 mg/kg/day in rats exposed by gavage for 21 days (NTP 1996), and hepatocellular degeneration in mice exposed to 337.5 mg/kg/day by gavage for 16 days (NTP 1993d) or 599 mg/kg/day in the diet for 15 days (NTP 2004a). The lowest LOAELs in these studies were 100–104 mg/kg/day for reduced body weight gain and hepatocyte cytoplasmic vacuolation in rats exposed by gavage (NCI 1978; NTP 1996) and 337.5 mg/kg/day for hepatocellular degeneration in mice exposed by gavage (NTP

1993d). The NTP (2004a) 14-week dietary study is the best basis for MRL derivation because it tested wider ranges of doses and varieties of end points, and identified lower LOAELs, than the other intermediate-duration studies.

Potential points of departure for the intermediate-duration oral MRL were derived by BMD analysis of the NTP (2004a) rat liver data in Table A-5. All available dichotomous models in the EPA Benchmark Dose Software (BMDS version 1.3.2) were fit to the incidence data for hepatocyte necrosis. The continuous-variable models in the software were applied to the data for changes in relative liver weight and serum ALT, SDH, bile acids, and cholesterol.

Table A-5. Selected Liver Effects in Rats Exposed to 1,1,2,2-Tetrachloroethane in the Diet for 14 weeks

	Dose (mg/kg/day)					
End point	0	20	40	80	170	320
Males (10/group)						
Liver weight						
relative (%)	34.79±0.42	36.72±0.44	41.03±0.85[b]	45.61±0.52[b]	44.68±0.45[b]	52.23±1.42[b]
Hepatocyte necrosis	0	0	0	0	8[b]	10[b]
Serum ALT (IU/L)	48±2	49±2	53±2	69±3[b]	115±8[b]	292±18[b]
Serum SDH (IU/L)	23±1	27±1[b]	26±2	31±1[b]	47±2[b]	74±4[b]
Bile acids (µmol/L)	29.2±2.9	27.5±2.7	27.2±2.7	35.9±3.9	92.0±16.6[b]	332.4±47.4[b]
Females (10/group)						
Liver weight						
relative (%)	35.07±0.56	36.69±0.36	37.84±0.51[b]	44.20±0.27[b]	48.03±0.89[b]	58.40±1.42[b]
Hepatocyte necrosis	0	0	0	1	7[b]	10[b]
Serum ALT (IU/L)	46±2	42±1	41±2	49±2	112±7[b]	339±18[b]
Serum SDH (IU/L)	27±1	27±1	28±2	25±1	45±3[b]	82±3[b]
Bile acids (µmol/L)	37.0±7.1	46.6±6.5	39.1±5.6	36.3±3.9	39.3±7.9	321.5±50.6[b]
Serum cholesterol (mg/dL)	104±4	105±3	98±1	81±2[b]	64±3[b]	55±3[b]

[a]Mean±standard error.
[b]Statistically significantly different from control value.

ALT = alanine aminotransferase; SDH = sorbitol dehydrogenase

Source: NTP 2004a

For the incidence data, predicted doses associated with 30, 20, 10, 5, and 1% extra risks were calculated as possible alternative BMRs for the best fitting model. Conventionally, a 10% extra risk has served as a point of departure for MRL determination. However, for a study that examined only 10 animals per group, the limit of detection is above the 10% level, likely in the 20–30% range. For the continuous data, the BMDs and the 95% lower confidence limits (BMDLs) calculated are estimates of the doses associated with a change of 1 standard deviation from the control. Predicted doses associated with an increase of

100% (i.e., 2-fold) were also calculated for the best fitting model for the changes in liver enzymes (ALT, SDH) in the serum, as an increase of this magnitude is sometimes considered to be an indicator of clinical significance for these effects. A summary of the predicted BMDs and BMDLs for all of the end points is shown in Table A-6.

Table A-6. Summary of BMD Model Predictions for Rats Exposed to 1,1,2,2-Tetrachloroethane in the Diet for 14 Weeks (Best Fitting Models)

End point	BMR	BMD (mg/kg/day)	BMDL (mg/kg/day)
Males			
Hepatocyte necrosis	10% extra risk	139.31	77.95
	1% extra risk	121.94	46.26
	5% extra risk	133.65	66.47
	20% extra risk	145.73	92.04
	30% extra risk	150.16	102.14
Relative liver weight	1 control standard deviation	No adequate fit to the data	
Serum ALT	1 control standard deviation	38.23	26.56
	100% relative deviation	134.06	121.35
Serum SDH	1 control standard deviation	36.71	25.13
	100% relative deviation	179.61	152.27
Bile acids	1 control standard deviation	72.45	57.17
Females			
Hepatocyte necrosis	10% extra risk	82.89	53.88
	1% extra risk	51.02	22.51
	5% extra risk	70.55	40.85
	20% extra risk	99.76	72.51
	30% extra risk	113.30	87.38
Relative liver weight	1 control standard deviation	No adequate fit to the data	
Serum ALT	1 control standard deviation	No adequate fit to the data	
Serum SDH	1 control standard deviation	No adequate fit to the data	
Bile acids	1 control standard deviation	216.74	177.00
Serum cholesterol	1 control standard deviation	No adequate fit to the data	

ALT = alanine aminotransferase; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; BMR = benchmark response; SDH = sorbitol dehydrogenase

Source: NTP 2004a

The lowest BMDLs were calculated for the male rat serum ALT and SDH data using 1 standard deviation below the control mean as the BMR. The BMDLs for serum ALT (26.56 mg/kg/day) and serum SDH (25.13 mg/kg/day) are approximately half of the BMDL of 53.88 mg/kg/day calculated using the female rat hepatocyte necrosis incidence data and a BMR of 10%. The BMDLs for the serum enzyme changes appear to be overly conservative predictions that have questionable biological plausibilty because they are substantially below the study NOAEL of 80 mg/kg/day. Effects occurring at the NOAEL included increases in serum ALT and SDH that were not biologically significant and hepatocyte necrosis in 1/10 females. The BMDL of 53.88 mg/kg/day for hepatocyte necrosis was selected as the point of

departure for the MRL because it is reasonably consistent with the observed findings. The intermediate-duration oral MRL of 0.5 mg/kg/day was derived by dividing the BMDL by a composite uncertainty factor of 100 (10 for extrapolation from humans and 10 for human variability).

Details of Benchmark Dose Analysis for the Intermediate-duration Inhalation MRL

Hepatocyte necrosis

All available dichotomous models in the EPA Benchmark Dose Software (BMDS version 1.3.2) were fit to the incidence data for hepatocyte necrosis in male and female rats (Table A-5). Predicted doses associated with 30, 20, 10, 5, and 1% extra risks were calculated for the best fitting models.

As assessed by the chi-square goodness-of-fit test, several models in the software provided adequate fits to the data for the incidence of hepatocyte necrosis in male rats (x^2 p-value ≥ 0.1) (Table A-2). Comparing across models, a better fit is indicated by a lower Akaike's Information Criteria value (AIC) (EPA 2000). The log-logistic model was determined to be the best-fitting model, as indicated by the AIC for the male rat data (Table A-7, Figure A-1), and the gamma model was determined to be the best fit to the female data (Table A-8, Figure A-2). Benchmark doses (BMDs and BMDLs) associated with an extra risk of 10% were calculated for all models. Alternative BMRs of 1, 5, 20, and 30% were calculated from the best fitting model for each data set. These are shown in Table A-6.

Table A-7. Goodness of Fit Statistics and BMD10s and BMDL10s from Models Fit to Incidence Data for Hepatocyte Necrosis in Male Rats Exposed to 1,1,2,2-Tetrachloroethane in the Diet for 14 Weeks

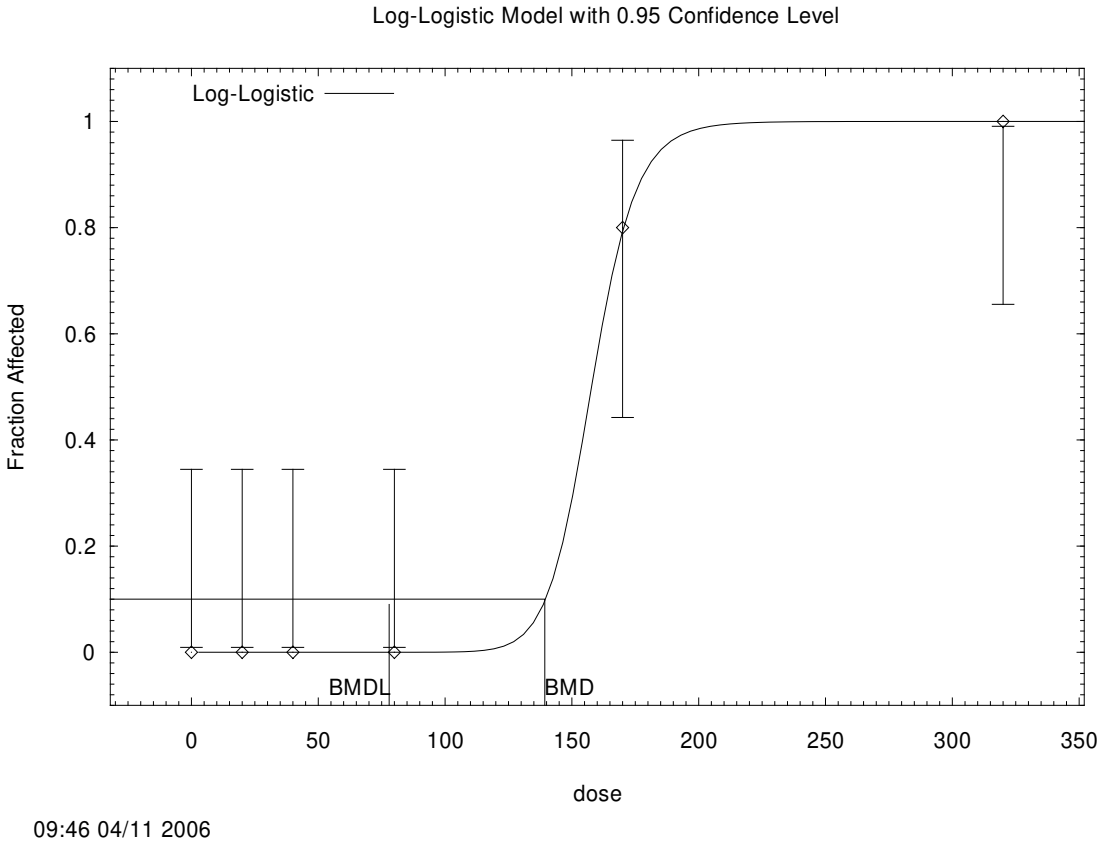
Model	Degrees of freedom	X^2 test statistic	X^2 p-value[a]	AIC	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)
Gamma[d]	5	12.30	0.9995	12.30	102.95	74.23
Logistic	4	0.00	1.0000	14.01	154.00	81.87
Log-Logistic[b,e]	5	0.00	1.0000	12.01	139.31	77.95
Multistage[c,f]	4	0.86	0.9304	13.59	88.60	65.67
Probit	4	0.00	1.0000	14.01	140.74	78.18
Log-probit[e]	4	0.00	1.0000	14.01	133.48	76.77
Quantal-linear	5	12.79	0.0255	32.82	20.50	13.77
Quantal-quadratic	5	4.56	0.4718	19.68	53.11	41.50
Weibull[d]	4	0.00	1.0000	14.01	144.11	76.51

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria
[b]Best-fitting model
[c]2-degree polynomial; lowest degree polynomial with adequate fit
[d]Power restricted to >=1
[e]Slope restricted to >=1
[f]Betas restricted to >=0

AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose

Source: NTP 2004a

Figure A-1. Observed and Predicted Incidences of Hepatocyte Necrosis in Male Rats Exposed to 1,1,2,2-Tetrachloroethane in the Diet for 14 Weeks*



*BMDs and BMDLs indicated are for a 10% extra risk and are in units of mg/kg/day.

Source: NTP 2004a

Table A-8. Goodness of Fit Statistics and BMD10s and BMDL10s from Models Fit to Incidence Data for Hepatocyte Necrosis in Female Rats Exposed to 1,1,2,2-Tetrachloroethane in the Diet for 14 Weeks

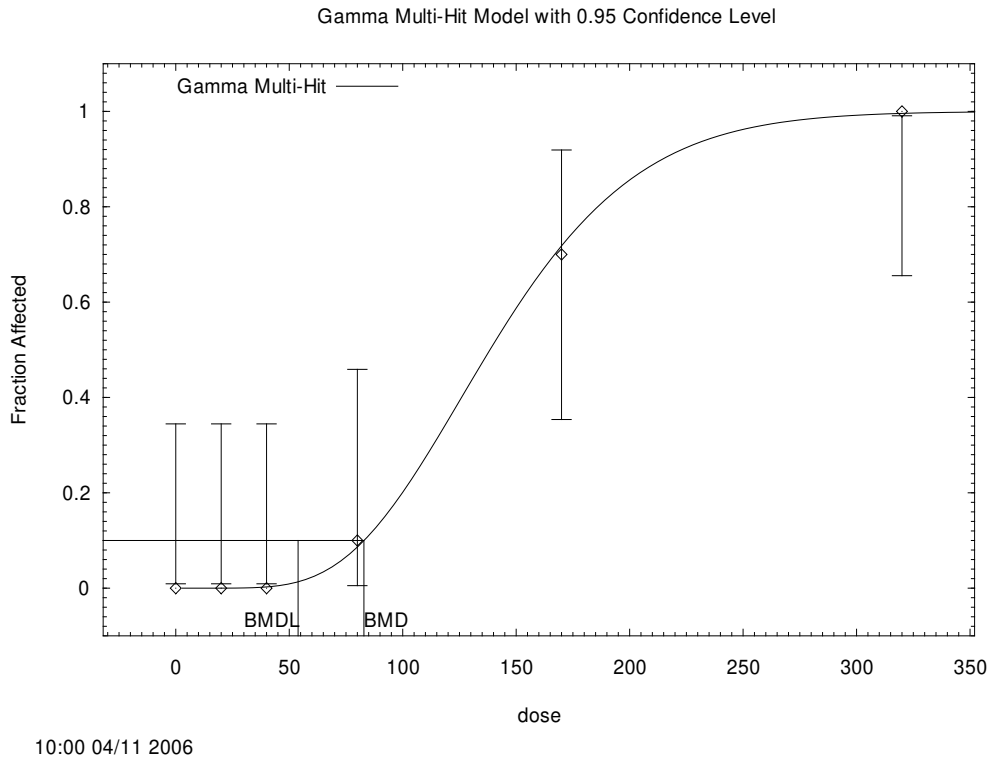
Model	Degrees of freedom	X^2 test statistic	X^2 p-value[a]	AIC	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)
Gamma[b,d]	4	0.11	0.9986	22.89	82.89	53.88
Logistic	4	0.47	0.9765	23.39	92.95	62.34
Log-Logistic[e]	4	0.36	0.9853	23.30	84.90	56.41
Multistage[c,f]	4	0.14	0.9978	22.95	84.75	49.88
Probit	4	0.24	0.9933	23.08	87.79	58.48
Log-probit[e]	4	0.20	0.9953	23.03	82.69	56.27
Quantal-linear	5	8.84	0.1156	34.83	20.87	14.04
Quantal-quadratic	5	1.80	0.8755	23.60	54.34	42.71
Weibull[d]	4	0.12	0.9983	22.92	84.37	51.46

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria
[b]Best-fitting model
[c]2-degree polynomial; lowest degree polynomial with adequate fit
[d]Power restricted to >=1
[e]Slope restricted to >=1
[f]Betas restricted to >=0

AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose

Source: NTP 2004a

Figure A-2. Observed and Predicted Incidences of Hepatocyte Necrosis in Female Rats Exposed to 1,1,2,2-Tetrachloroethane in the Diet for 14 Weeks*



*BMDs and BMDLs indicated are for a 10% extra risk and are in units of mg/kg/day.

Source: NTP 2004a

Continuous Data

Available continuous-variable models in the EPA Benchmark Dose Software (linear, polynomial, power, and Hill models; BMDS version 1.3.2) were fit to the data shown in Table A-5, for changes in relative liver weight and serum ALT, SDH, bile acids and cholesterol in male and female rats. The BMDs and the 95% lower confidence limits (BMDLs) calculated are estimates of the doses associated with a change of 1 standard deviation from the control. Predicted doses associated with an increase of 100% were also calculated for the changes in serum liver enzymes. For the continuous data, the simplest model (linear) was applied to the data first while assuming constant variance. If the data were consistent with the assumption of constant variance (p-value $\geq$0.1), then the fit of the linear model to the means was evaluated. If the linear model adequately fit the means (p-value $\geq$0.1), then it was selected as the model for BMD derivation. If the linear model did not adequately fit the means, then the more complex models were fit to the data while assuming constant variance. Among those providing adequate fit to the means (p-value $\geq$0.1), the one with the lowest AIC for the fitted model was selected for BMD derivation. If the test for constant variance was negative, the linear model was run again while applying the power model integrated into the BMDS to account for non-homogenous variance. If the non-homogenous variance model provided an adequate fit (p-value $\geq$0.1) to the variance data, then the fit of the linear model to the

means was evaluated. If the linear model did not provide adequate fit to the means while the variance model was applied, then the polynomial, power, and Hill models were fit to the data and evaluated while the variance model was applied. Among those providing adequate fit to the means (p-value ≥0.1), the one with the lowest AIC for the fitted model was selected for BMD derivation. If the test for constant variance was negative and the non-homogenous variance model did not provide an adequate fit to the variance data, then the data set was considered not to be suitable for BMD modeling.

Relative liver weight

Statistical tests indicated that variances were not constant across exposure groups (this is reflected in the standard errors listed in Table A-5). The non-homogeneous variance model did not adequately fit the variance data for either males or females; therefore, there was no good fit to the data for change in relative liver weight in either male or female rats (Table A-9).

Table A-9. Model Predictions for Changes in Relative Liver Weight in Rats Exposed to 1,1,2,2-Tetrachloroethane in the Diet for 14 Weeks

Model	Variance p-value[a]	Means p-value[b]	BMD_{1sd} (mg/kg/day)	$BMDL_{1sd}$ (mg/kg/day)
Male				
Linear (constant variance)	<0.0001	<0.0001	68.02	56.64
Linear (modeled variance)	0.0255	<0.0001	55.05	37.77
Female				
Linear (constant variance)	<0.0001	0.0063	36.16	30.95
Linear (modeled variance)	0.0076	0.0004	22.21	14.61

[a]Values <0.05 fail to meet conventional goodness-of-fit criteria
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria

BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose

Source: NTP 2004a

Serum ALT

For the serum ALT data, the assumption of constant variance did not hold for either the male or female data. The non-homogeneous variance model was applied and provided adequate fit to the variance for both the male and female data. With the variance model applied, the linear model did not provide adequate fit to the means for either the male or female data. For the males, both the polynomial and power models provided adequate fit to the means while the variance model was applied. The AIC was slightly lower for the polynomial model, which was selected as the best fitting model. Doses associated with a 100% change from the control (2-fold) from the polynomial model were also calculated (Table A-10, Figure A-3). For the females, none of the models were able to provide adequate fit to the means while the variance model was applied.

Table A-10. Model Predictions for Changes in Serum ALT in Rats Exposed to 1,1,2,2-Tetrachloroethane in the Diet for 14 Weeks

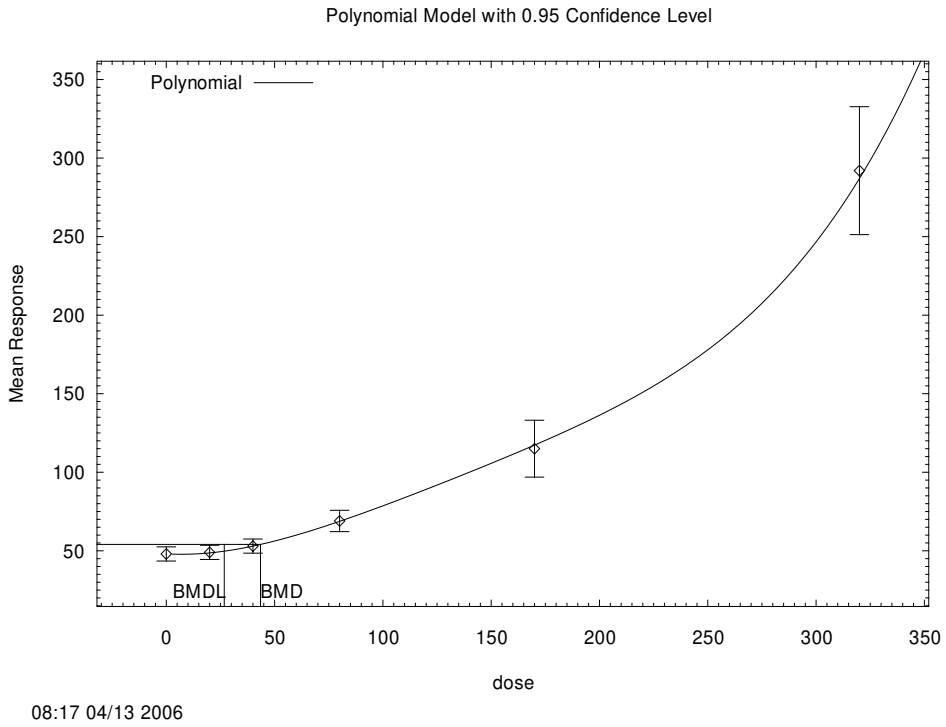
Model	BMR	Variance p-value[a]	Means p-value[b]	AIC	BMD (mg/kg/day)	BMDL (mg/kg/day)
Male						
Linear (constant variance)	1 sd	<0.0001	<0.0001	484.88	43.91	37.37
Linear (modeled variance)	1 sd	0.7223	<0.0001	412.89	12.72	10.07
Polynomial[c,d] (modeled variance)	1 sd	0.7223	0.7302	367.955	38.23	26.56
	100%	0.7223	0.7302	367.955	134.06	121.35
Power[e] (modeled variance)	1 sd	0.6731	0.7945	367.956	41.97	32.24
Hill[f] (modeled variance)	NA					
Female						
Linear (constant variance)	1 sd	<0.0001	<0.0001	511.01	44.94	38.22
Linear (modeled variance)	1 sd	0.1849	<0.0001	447.29	17.59	13.50
Polynomial[g] (modeled variance)	1 sd	0.1849	<0.0001	370.32	49.47	45.00
Power[e] (modeled variance)	1 sd	0.1782	0.0074	358.41	64.68	56.13
Hill[f] (modeled variance)	NA					

[a]Values <0.05 fail to meet conventional goodness-of-fit criteria
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria
[c]Best-fitting model
[d]2-degree polynomial; lowest degree polynomial with adequate fit
[e]Power restricted to >=1
[f]N restricted to >1
[g]2-degree polynomial; no adequate fit with any polydegree

AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; NA = not available (BMD software could not generate a model output); sd = standard deviation

Source: NTP 2004a

Figure A-3. Changes in Serum ALT in Male Rats Exposed to 1,1,2,2-Tetrachloroethane in the Diet for 14 Weeks*



*BMDs and BMDLs indicated are associated with a change of 1 standard deviation from the control, and are in units of mg/kg/day.

Source: NTP 2004a

Serum SDH

For the serum SDH data, the assumption of constant variance did not hold for either the male or female data. The non-homogeneous variance model was applied and provided marginally adequate fit to the variance for both the male and female data. With the variance model applied, the linear model did not provide adequate fit to the means for either the male or female data. For the males, both the polynomial and power models provided adequate fit to the means while the variance model was applied. The AIC was slightly lower for the polynomial model, which was selected as the best fitting model. Doses associated with a 100% change from the control (2-fold) from the polynomial model were also calculated (Table A-11, Figure A-4). For the females, none of the models were able to provide adequate fit to the means while the variance model was applied.

Table A-11. Model Predictions for Changes in Serum SDH in Rats Exposed to 1,1,2,2-Tetrachloroethane in the Diet for 14 Weeks

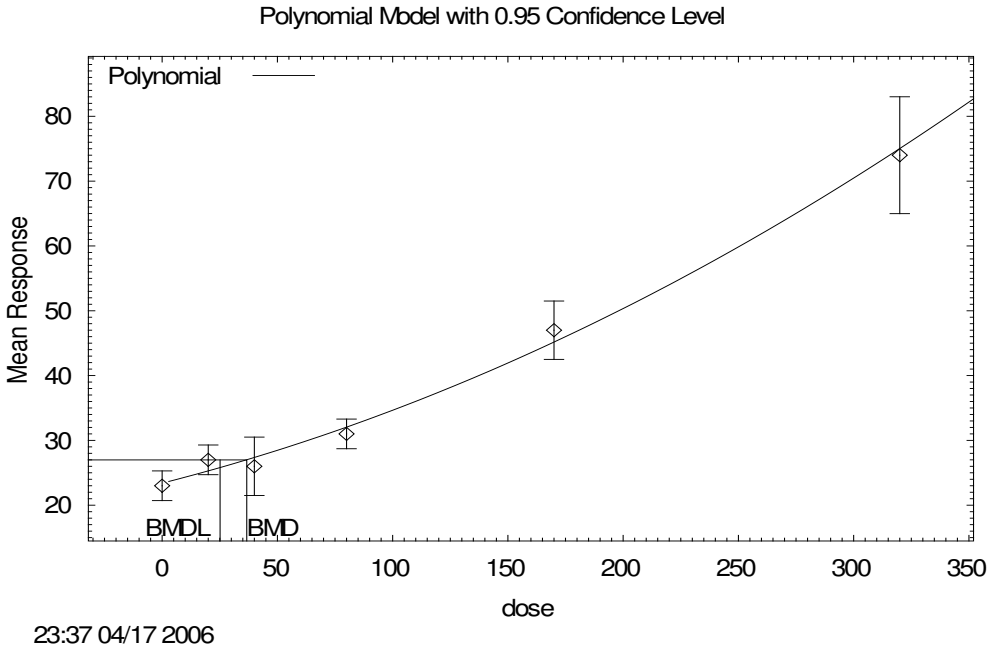
Model	BMR	Variance p-value[a]	Means p-value[b]	AIC	BMD (mg/kg/day)	BMDL (mg/kg/day)
Male						
Linear (constant variance)	1 sd	<0.0001	0.1889	291.96	41.70	35.55
Linear (modeled variance)	1 sd	0.0499	0.0471	274.89	23.86	19.11
Polynomial[c,d] (modeled variance)	1 sd	0.0499	0.3259	270.72	36.70	25.13
	100%	0.0499	0.3259	270.72	179.61	152.27
Power[e] (modeled variance)	1 sd	0.0499	0.3044	270.89	44.40	28.51
Hill[f] (modeled variance)	NA					
Female						
Linear (constant variance)	1 sd	<0.0001	<0.0001	319.64	47.70	40.47
Linear (modeled variance)	1 sd	0.0429	<0.0001	310.32	34.45	26.54
Polynomial[g] (modeled variance)	1 sd	0.0429	0.0018	283.22	92.47	69.39
Power[e] (modeled variance)	1 sd	0.0429	0.0018	285.20	90.68	70.92
Hill[f] (modeled variance)	NA					

[a]Values <0.05 fail to meet conventional goodness-of-fit criteria
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria
[c]Best-fitting model
[d]2-degree polynomial; lowest degree polynomial with adequate fit
[e]Power restricted to >=1
[f]N restricted to >1
[g]2-degree polynomial; no adequate fit with any polydegree

AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; NA = not available (BMD software could not generate a model output); sd = standard deviation

Source: NTP 2004a

Figure A-4. Changes in Serum SDH in Male Rats Exposed to 1,1,2,2-Tetrachloroethane in the Diet for 14 Weeks*



*BMDs and BMDLs indicated are associated with a change of 1 standard deviation from the control, and are in units of mg/kg/day.

Source: NTP 2004a

Bile acids

For the serum bile acids data, the assumption of constant variance did not hold for either the male or female data. The non-homogeneous variance model was applied and provided adequate fit to the variance for both the male and female data. With the variance model applied, the Linear and Hill models did not provide adequate fit to the means for either the male or female data, and the Polynomial model did not provide adequate fit to the mean for the female data. For the males, both the Polynomial and Power models provided adequate fit to the means while the variance model was applied. The Power model was selected as the best fitting model for the male data because it had a slightly lower AIC than the Polynomial model (Table A-12, Figure A-5). For the females, the Power model was the only model that provided adequate fit to the means while the variance model was applied (Table A-12, Figure A-6).

Table A-12. Model Predictions for Changes in Bile Acids in Rats Exposed to 1,1,2,2-Tetrachloroethane in the Diet for 14 Weeks

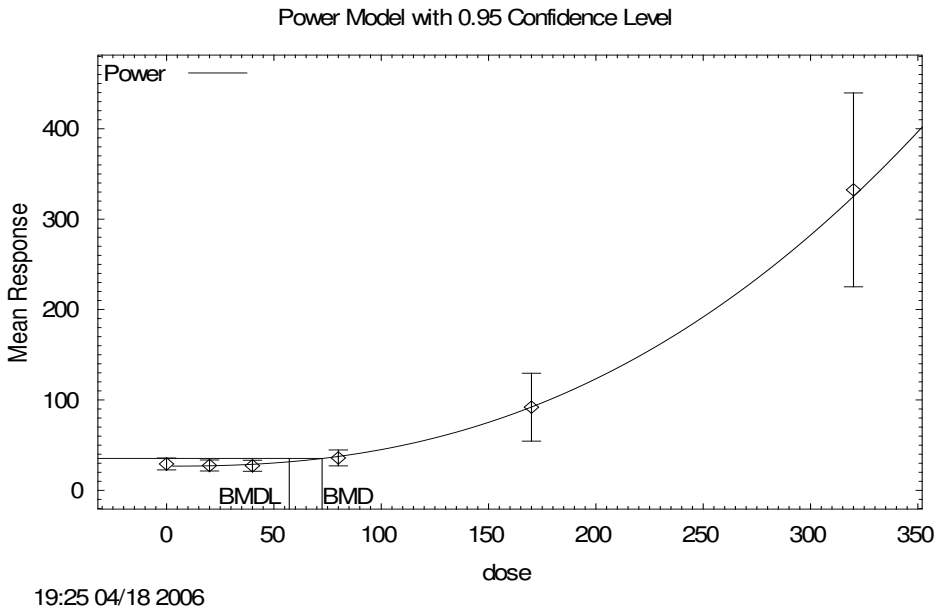
Model	BMR	Variance p-value[a]	Means p-value[b]	AIC	BMD (mg/kg/day)	BMDL (mg/kg/day)
Male						
Linear (constant variance)	1sd	<0.0001	0.0013	577.11	79.44	61.93
Linear (modeled variance)	1sd	0.7661	<0.0001	464.43	24.81	20.06
Polynomial[c] (modeled variance)	1sd	0.7661	0.1194	428.95	58.37	49.57
Power[d,e] (modeled variance)	1sd	0.7661	0.4582	427.70	72.45	57.17
Hill[f] (modeled variance)	NA					
Female						
Linear (constant variance)	1sd	<0.0001	<0.0001	594.57	101.36	81.28
Linear (modeled variance)	1sd	0.4663	<0.0001	576.14	NA	54.83
Polynomial[g] (modeled variance)	1sd	0.4663	<0.0001	487.96	149.50	106.40
Power[d,e] (modeled variance)	1sd	0.4663	0.3751	466.68	216.74	177.00
Hill[f] (modeled variance)	NA					

[a]Values <0.05 fail to meet conventional goodness-of-fit criteria
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria
[c]2-degree polynomial; lowest degree polynomial with adequate fit
[d]Best-fitting model
[e]Power restricted to >=1
[f]N restricted to >1
[g]2-degree polynomial; no adequate fit with any polydegree

AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; NA = not available (BMD software could not generate a model output)

Source: NTP 2004a

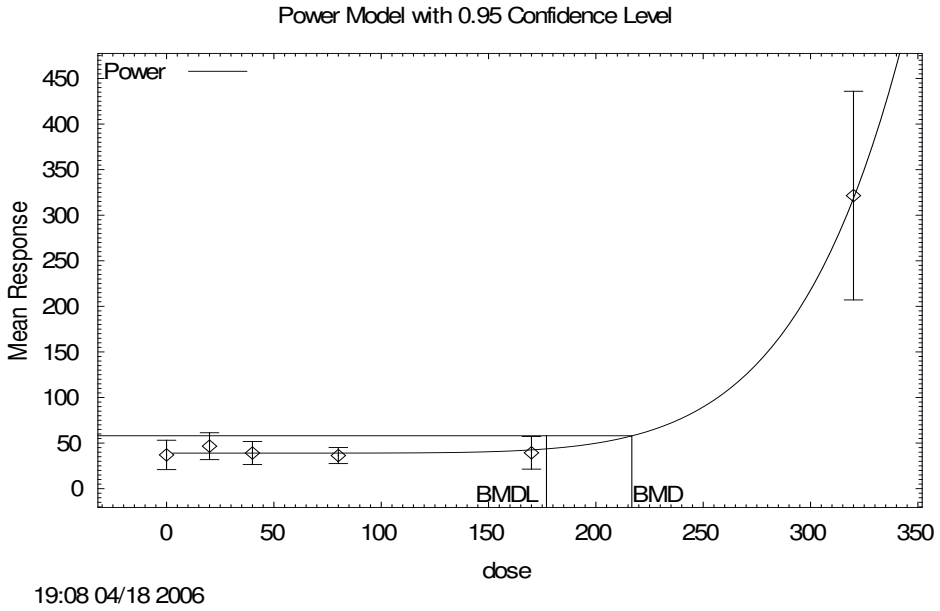
Figure A-5. Changes in Bile Acids in Male Rats Exposed to 1,1,2,2-Tetrachloroethane in the Diet for 14 Weeks*



*BMDs and BMDLs indicated are associated with a change of 1 standard deviation from the control, and are in units of mg/kg/day.

Source: NTP 2004a

Figure A-6. Changes in Bile Acids in Female Rats Exposed to 1,1,2,2-Tetrachloroethane in the Diet for 14 Weeks*



*BMDs and BMDLs indicated are associated with a change of 1 standard deviation from the control, and are in units of mg/kg/day.

Source: NTP 2004a

Serum cholesterol (females only)

Statistical tests indicated that variances were not constant across exposure groups (this is reflected in the standard deviations listed in Table A-5). The non-homogeneous variance model did not adequately fit the variance data; therefore, there was no good fit to the data for change in serum cholesterol in female rats (Table A-13).

Table A-13. Model Predictions for Changes in Serum Cholesterol in Female Rats Exposed to 1,1,2,2-Tetrachloroethane in the Diet for 14 Weeks

Model	Variance p-value[a]	Means p-value[b]	BMD_{1sd} (mg/kg/day)	$BMDL_{1sd}$ (mg/kg/day)
Female				
Linear (constant variance)	0.0044	<0.0001	63.66	53.24
Linear (modeled variance)	0.0019	<0.0001	56.37	39.96

[a]Values <0.05 fail to meet conventional goodness-of-fit criteria
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria

BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose

Source: NTP 2004a

Agency Contacts (Chemical Managers): Jessilynn Taylor, Henry Abadin, and Eugene Demchuk

APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not

meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system,

which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

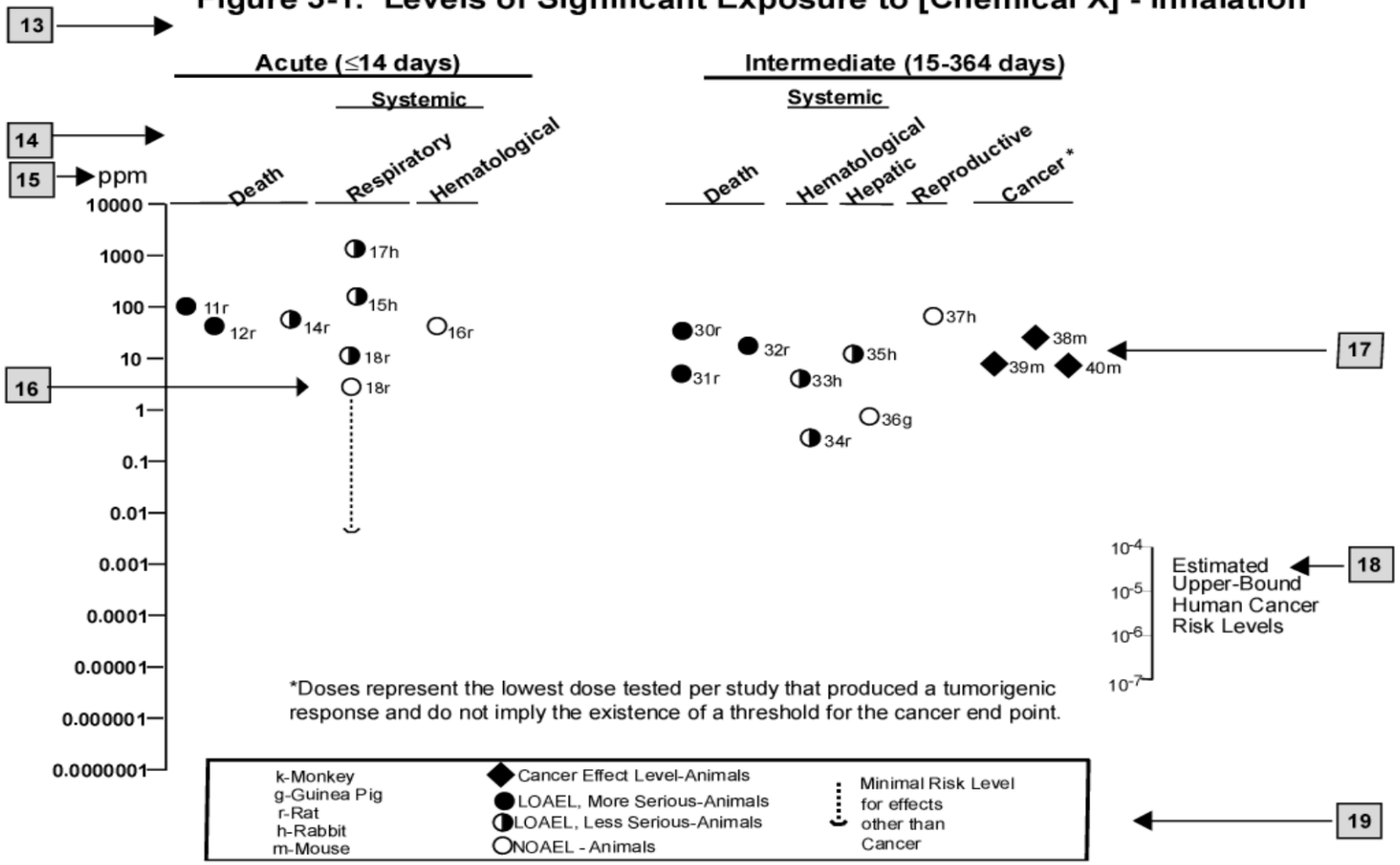
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
4 →							
CHRONIC EXPOSURE							
Cancer					11		
					↓		
38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD	benchmark dose
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation

APPENDIX C

DOT/UN/ NA/IMDG	Department of Transportation/United Nations/ North America/Intergovernmental Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level

MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water

OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

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APPENDIX D. INDEX