DRAFT
TOXICOLOGICAL PROFILE FOR
1,1,1-TRICHLOROETHANE

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

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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 1,1,1-Trichloroethane was released in 1995. 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/Toxicology Information Branch
1600 Clifton Road NE,
Mailstop F-32
Atlanta, Georgia 30333

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. We plan to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Comments should be sent to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road, N.E.
Mail Stop F-32
Atlanta, Georgia 30333

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 November 7, 2003 (68 FR 63098). 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) and October 25, 2001 (66 FR 54014) . Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

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

Julie Louise Gerberding, M.D., M.P.H.
Administrator
Agency for Toxic Substances and
Disease Registry

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: 1-888-42-ATSDR or (404) 498-0110 ***Fax:*** (770) 488-4178
E-mail: atsdric@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, 55 West Seegers Road, Arlington Heights, IL 60005 • Phone: 847-818-1800 • FAX: 847-818-9266.

CONTRIBUTORS

CHEMICAL MANAGER(S)/AUTHOR(S):

Alfred F. Dorsey, D.V.M.
Henry G. Abadin, M.S.P.H.
Daphne B. Moffett, Ph.D.
ATSDR, Division of Toxicology, Atlanta, GA

David W. Wohlers, Ph.D.
Mona Singh, Ph.D.
Syracuse Research Corporation, North Syracuse, NY

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 Research Implementation Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

PEER REVIEW

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

1. Dr. Bhupendra Kaphalia, Associate Professor, Department of Pathology, University of Texas Medical Branch, Galveston Texas;

2. Dr. Kannan Krishnan, Professor and Director, Human Toxicology Research Group, University of Montreal, Pierrefonds, PQ, Canada;

3. Dr. Gary Stoner, Professor, Environmental Health Sciences, Ohio State University School of Public Health, Columbus, Ohio;

These experts collectively have knowledge of 1,1,1-trichloroethane'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. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

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 1,1,1-trichloroethane (also called 1,1,1-TCE) and the effects of exposure to it.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. EPA then places these sites on the National Priorities List (NPL) and targets them for federal long-term cleanup activities. 1,1,1-TCE has been found in at least 809 of the 1,647 current or former NPL sites. Although the total number of NPL sites evaluated for this substance is not known, the number of sites at which 1,1,1-TCE is found could increase as more sites are evaluated. This information is important because these sites may be sources of exposure, and exposure to this substance can harm you.

When a substance is released either from a large area, such as an industrial plant, or 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 contact it—by breathing, eating, or drinking the substance or by skin contact.

Many factors will determine whether exposure to 1,1,1-TCE will harm you. These factors include the dose (how much), the duration (how long), and the way you contacted it. You also must consider any other chemicals to which you are exposed and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT IS 1,1,1-TRICHLOROETHANE?

1,1,1-TCE is a synthetic chemical that does not occur naturally in the environment. It also is known as methylchloroform, methyltrichloromethane, trichloromethylmethane, and α-trichloro-methane. Its registered trade names are chloroethene NU® and Aerothene TT®. It is a colorless liquid with a sweet, sharp odor. 1,1,1-TCE dissolves slightly in water. The liquid evaporates quickly and becomes a vapor. Most people begin to smell 1,1,1-TCE in the air when its levels

reach 120 –500 parts per million (ppm). If the chemical makes up 8–10.5% (80,000–105,000 ppm) of the air, it can burn easily when it contacts a spark or flame. A poisonous gas known as phosgene can be produced during welding if 1,1,1-TCE is used to clean the metal. 1,1,1-TCE also can be found in soil and water, particularly at hazardous waste sites. Because of its tendency to evaporate easily, the vapor form is most commonly found in the environment.

1,1,1-TCE was used in commercial products, mostly to dissolve other chemicals. About 800 million pounds were produced in 1990, but less than 500 million pounds are being made today. No 1,1,1-TCE is supposed to be manufactured for domestic use in the United States after January 1, 2002 because it affects the ozone layer. Most of 1,1,1-TCE that is manufactured today is exported to developing countries. 1,1,1-TCE had many industrial and household uses. It often was used as a solvent to dissolve other substances, such as glues and paints. In industry, it was used widely to remove oil or grease from manufactured metal parts. In the home, it used to be an ingredient of products such as spot cleaners, glues, and aerosol sprays.

You will find detailed information about the chemical properties of 1,1,1-TCE in Chapter 4. Chapter 5 describes production data and the uses of 1,1,1-TCE.

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

Most of the 1,1,1-TCE released into the environment enters the air, where it lasts for about 6 years. Once in the air, it can travel to the upper part of the earth's atmosphere, which is called the stratosphere. There, sunlight breaks it down into other chemicals that may reduce the stratospheric ozone layer. This ozone layer blocks certain damaging ultraviolet rays of the sun from reaching the earth's surface. Some scientists think the gradual thinning of the ozone layer is increasing the number of skin cancer cases in humans.

Spills, improper disposal, industrial emissions, and consumer use can release large amounts of 1,1,1-TCE into the environment. Contaminated water from landfills and hazardous waste sites can contaminate surrounding soil and nearby surface water or groundwater. However, most of

the chemical probably will evaporate eventually into the air. It will not build up in plants or animals. Industrial operations release the largest amount of 1,1,1-TCE into the environment, mostly by emissions into the air. The vapor also enters the air because many products containing the chemical are used in the home and workplace.

We do not know how long 1,1,1-TCE lasts in water or soil. In surface waters, such as lakes and rivers, where it partially mixes with water, much of the chemical evaporates quickly. 1,1,1-TCE also evaporates from soil surfaces. Water can easily carry it through soil into groundwater. 1,1,1-TCE in groundwater can evaporate and pass through soil as a gas and finally be released to the air. Also, organisms that live in soil and water may break down 1,1,1-TCE. One study suggests that half of the chemical takes 200–300 days to break down in contaminated groundwater. However, the number of days can vary widely, depending on specific site conditions.

Chapter 6 provides further information about what happens to 1,1,1-TCE in the environment.

1.3 HOW MIGHT I BE EXPOSED TO 1,1,1-TRICHLOROETHANE?

You are not likely to be exposed to large enough amounts of 1,1,1-TCE to cause adverse health effects. 1,1,1-TCE has been found in air samples taken from all over the world. In the United States, city air typically contains about 0.1–1.0 parts per billion (ppb) of 1,1,1-TCE; rural air usually contains less than 0.1 ppb. Because 1,1,1-TCE was used so frequently in home and office products, much more was found in the air inside buildings (0.3–4.4 ppb) than in the outside air (0.1–0.9 ppb). Since this chemical was found in many building materials, new buildings used to have higher indoor levels than old buildings. Thus, you were likely to be exposed to 1,1,1-TCE vapor at higher levels indoors than outdoors or near hazardous waste sites. However, since 2002, 1,1,1-TCE is not expected to be commonly used, and therefore, the likelihood of being exposed to it is remote.

Common consumer products that used to contain 1,1,1-TCE included glues, household cleaners, and aerosol sprays. In the workplace, you could have been exposed to 1,1,1-TCE while using some metal degreasing agents, paints, glues, and cleaning products. You could have been exposed to 1,1,1-TCE by breathing the vapors from these products or by letting the liquid contact your skin. High levels of exposure have occurred in people who deliberately inhaled the vapors, as in glue-sniffing or solvent abuse.

1,1,1-TCE has been found in rivers and lakes (up to 0.01 ppm), in soil (up to 120 ppm), in drinking water (up to 0.0035 ppm), and in drinking water from underground wells (up to 5.4 ppm). In one case, drinking water from a private well contained up to 12 ppm, possibly as a result of illegal discharge or spill from a nearby industrial plant. Releases during manufacture and transportation and during industrial or household use can cause these high levels, but the levels vary substantially from one location to another. Certain foods you eat and water you drink or bathe in may be contaminated with 1,1,1-TCE. However, you can be exposed to 1,1,1-TCE primarily by drinking contaminated water and eating contaminated food. Chapter 6 discusses further information about human exposure to 1,1,1-TCE.

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

1,1,1-TCE can quickly enter your body if you breathe in air containing it in vapor form. It also enters your body if you drink water or eat food containing 1,1,1-TCE. If you spill 1,1,1-TCE on your skin, most of it quickly evaporates into the air, but small amounts enter your body through your skin. Regardless of how 1,1,1-TCE enters your body, nearly all of it quickly leaves your body in the air you exhale. The small amount that is not breathed out can be changed in your body into other substances, known as metabolites. Most of the metabolites leave your body in the urine and breath within a few days. Chapter 3 provides further information about how 1,1,1-TCE can enter and leave the body.

1.5 HOW CAN 1,1,1-TRICHLOROETHANE AFFECT MY HEALTH?

Scientists use many tests to protect the public from harmful effects of toxic chemicals and to find ways to treat people who have been harmed.

One way to learn whether a chemical will harm people is to determine how the body absorbs, uses, and releases the chemical. For some chemicals, animal testing may be necessary. Animal testing can help identify health problems such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method for getting information needed to make wise decisions that protect public health. Scientists have the responsibility to treat research animals with care and compassion. Scientists must comply with strict animal-care guidelines because laws today protect the welfare of research animals.

If you breathe air containing high levels of 1,1,1-TCE (1,000 ppm or higher) for a short time, you may become dizzy and lightheaded and possibly lose your coordination. These effects rapidly disappear after you stop breathing contaminated air. If you breathe in much higher levels of 1,1,1-TCE, either intentionally or accidentally, you may become unconscious, your blood pressure may decrease, and your heart may stop beating. Whether breathing low levels of 1,1,1-TCE for a long time causes harmful effects is not known. Studies in animals show that breathing air that contains very high levels of 1,1,1-TCE (higher than 2,000 ppm) damages the breathing passages and causes mild effects in the liver, in addition to affecting the nervous system. There are no studies in humans that determine whether eating food or drinking water contaminated with 1,1,1-TCE could harm health. Placing large amounts of 1,1,1-TCE in the stomachs of animals has caused effects on the nervous system, mild liver damage, unconsciousness, and even death. If your skin contacts 1,1,1-TCE, you might feel some irritation. Studies in animals suggest that repeated exposure of the skin might affect the liver and that very large amounts on the skin can cause death. These effects occurred only when evaporation was prevented.

Available information does not indicate that 1,1,1-TCE causes cancer. The International Agency for Research on Cancer (IARC) has determined that 1,1,1-TCE is not classifiable as to its

carcinogenicity in humans. EPA has also determined that 1,1,1-TCE is not classifiable as to its human carcinogenicity. The likelihood is very low that exposure to 1,1,1-TCE levels found near hazardous waste sites would cause significant health effects. You can find more information about the health effects of 1,1,1-TCE in Chapter 3.

1.6 HOW CAN 1,1,1-TRICHLOROETHANE AFFECT CHILDREN?

This section discusses potential health problems in people from exposures during conception to maturity (18 years of age).

Children exposed to large amounts of 1,1,1-TCE probably would be affected in the same manner as adults (see Section 1.5). In animals, it has been shown that 1,1,1-TCE can pass from the mother's blood into a fetus. When pregnant mice were exposed to high levels of 1,1,1-TCE in air, their babies developed more slowly than normal and had some behavioral problems. However, whether similar effects occur in humans has not been demonstrated.

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

If your doctor finds you (or a family member) have been exposed to substantial amounts of 1,1,1-TCE, ask whether your children also might have been exposed. Your doctor might need to ask your state health department to investigate.

Children can be exposed to 1,1,1-TCE in household products, such as adhesives and cleaners. Parents should store household chemicals out of reach of young children to prevent accidental poisonings or skin irritation. Always store household chemicals in their original labeled containers. Never store household chemicals in containers that children would find attractive to eat or drink from, such as old soda bottles. Keep your Poison Control Center's number near the phone.

Sometimes older children sniff household chemicals in an attempt to get high. Your children may be exposed to 1,1,1-TCE by inhaling products containing it. Talk with your children about the dangers of sniffing chemicals.

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

Samples of your breath, blood, and urine can be tested to determine if you have recently been exposed to 1,1,1-TCE. In some cases, these tests can estimate how much 1,1,1-TCE has entered your body. To be of any value, samples of your breath or blood have to be taken within hours after exposure, and samples of urine have to be taken within 2 days after exposure. However, these tests will not tell you whether your health will be affected by exposure to 1,1,1-TCE. The exposure tests are not routinely available in hospitals and clinics because they require special analytical equipment. See Chapters 3 and 7 for more information about tests for exposure to 1,1,1-TCE.

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. 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) of the Centers for Disease Control and Prevention (CDC) are two federal organizations that develop recommendations for toxic substances.

Regulations and recommendations can be expressed as “not-to-exceed” levels—in other words, levels of a toxic substance in air, water, soil, or food that do not exceed critical levels that usually are based on levels that affect animals; they are then adjusted to levels that will help protect

people. Sometimes these not-to-exceed levels differ among federal agencies because the agencies use different exposure times (for example, an 8-hour workday or a 24-hour day), different animal studies, or other factors.

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

EPA regulates the levels of 1,1,1-TCE that are allowable in drinking water. The highest level of 1,1,1-TCE allowed in drinking water is 0.2 ppm. EPA has determined that the level of 1,1,1-TCE in lakes and streams should not be more than 18 ppm. This level is not expected to result in harmful health effects from drinking water or eating fish contaminated with 1,1,1-TCE. Any releases or spills of 1,1,1-TCE of 1,000 pounds or more must be reported to the National Response Center. OSHA regulates 1,1,1-TCE levels in the workplace. The workplace exposure limit for an 8-hour workday, 40-hour workweek is 350 ppm in air. See Chapter 8 for more information about regulations and advisories regarding 1,1,1-TCE.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have 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 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 1-888-42ATSDR (1-888-422-8737), by e-mailing atsdric@cdc.gov, or by writing to

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

For-profit organizations can request copies of final Toxicological Profiles from

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 1,1,1-TRICHLOROETHANE IN THE UNITED STATES

1,1,1-Trichloroethane is a synthetic chemical. In 2003, the estimated capacity of the commercial production of 1,1,1-trichloroethane in the United States was 510 million pounds. Under the Clean Air Act as amended in 1990, all production of 1,1,1-trichloroethane for domestic use was scheduled to cease as of January 1, 2002. It may be used for essential applications such as medical devices and aviation safety (for the testing of metal fatigue and corrosion of existing airplane engines and other parts susceptible to corrosion) until January 1, 2005 or for export to developing countries until January 1, 2012. 1,1,1-Trichloroethane was predominantly used as a chemical intermediate in the manufacture of hydrochlorofluorocarbons (HCFCs). It was also commonly used in vapor degreasing and cold cleaning, adhesives, coatings and inks, textiles, and electronics.

1,1,1-Trichloroethane was released to the environment during the course of its manufacture, formulation, and use. It was frequently detected in the atmosphere and in water. In 2002, environmental releases of 1,1,1-trichloroethane reported under the EPA Toxics Release Inventory (TRI) program were about 234 thousand pounds in air emissions, 99 pounds in water discharges, 12 pounds in underground injection discharges, and 39 thousand pounds in releases to land.

Monitoring studies of the ambient air levels of 1,1,1-trichloroethane in urban areas have reported concentrations in the range of 0.1–1 ppb, while the concentrations in rural areas have been reported to be <0.1 ppb (Table 6-3). Representative data taken from five geographic areas located throughout the United States report indoor concentrations of 0.3–4.4 ppb and outdoor concentrations of 0.11–0.92 ppb. A more recent EPA region V (Minnesota, Wisconsin, Michigan, Illinois, Indiana, and Ohio) National Human Exposure Assessment Survey (NHEXAS) detected a mean concentration of 1,1,1-trichloroethane to be 1.15 ppb in indoor air samples collected from residential areas from July 1995 to May 1997.

Levels of 1,1,1-trichloroethane detected in water ways near sources of emissions such as industrial waste water, hazardous waste sites, and spill locations are usually <1 ppb. Drinking water from surface or groundwater sources contained 1,1,1-trichloroethane concentrations of 0.01–3.5 ppb. Limited monitoring

data are available for the presence of 1,1,1-trichloroethane in soil. 1,1,1-Trichloroethane is expected to rapidly volatilize from soil and to leach through soil.

Environmental exposures of humans to 1,1,1-trichloroethane have been correlated with levels of parent compound and 1,1,1-trichloroethane metabolites (trichloroethanol and trichloroacetic acid) in expired air, blood, and urine. The appearance of trichloroacetic acid in urine is not unique to 1,1,1-trichloroethane, as it has also been identified as a urinary metabolite of trichloroethylene and tetrachloroethylene. If exposure is known to be solely to 1,1,1-trichloroethane, trichloroacetic acid levels in the urine may be a useful biomarker of exposure, because of the relatively long half-life of trichloroacetic acid. However, the length of time between 1,1,1-trichloroethane exposure and the measurement of breath, blood, or urine levels is critical to the accurate evaluation of the magnitude of exposure. Up to 90% of the 1,1,1-trichloroethane absorbed by any route is rapidly excreted unchanged in the expired air. Most of the remaining 10% is accounted for as the urinary metabolites trichloroethanol and trichloroacetic acid.

2.2 SUMMARY OF HEALTH EFFECTS

1,1,1-Trichloroethane is one of many solvents inhaled by some people to alter mood or consciousness. Available human and animal data indicate that the central nervous system is the most sensitive target for 1,1,1-trichloroethane toxicity. Clinical signs of toxicity associated with human exposure to large quantities of 1,1,1-trichloroethane include central nervous system depression, hypotension, cardiac arrhythmia, diarrhea and vomiting, mild hepatic effects, and dermal and ocular irritation. Deaths of persons exposed to high concentrations have been attributed to cardiac arrhythmia and respiratory failure secondary to central nervous system depression. Lower-level exposure to 1,1,1-trichloroethane may result in more subtle neurological effects such as impaired performance in tests designed to measure variables such as manual dexterity, eye-hand coordination, perceptual speed, and reaction time. Mild hepatotoxicity has been demonstrated in some animals exposed to relatively large quantities of 1,1,1-trichloroethane. Mild developmental effects induced by high level exposure of animals have not been verified in humans. Available data are inadequate to determine the carcinogenicity of 1,1,1-trichloroethane. The EPA has classified 1,1,1-trichloroethane as group D, not classifiable as to human carcinogenicity, based on no reported human data and inadequate animal data. In general, route of exposure does not appear to be as important as circulating levels of 1,1,1-trichloroethane.

Death. The volatility of 1,1,1-trichloroethane, in addition to the rapid and extensive absorption and elimination of the inhaled compound, makes acute inhalation in product use situations the most likely lethal exposure scenario in humans. The acute lethal air concentration for humans is unknown; however, simulations of several lethal exposures suggest that it may be as low as 6,000 ppm. The results of animal studies indicate that the acute lethal exposure concentration decreases substantially with increasing exposure duration. Thus, the concentration required to cause animal death after a 6–7-hour exposure is 3–4 times less than that required after a 15-minute exposure.

Human deaths after inhalation exposure to 1,1,1-trichloroethane have been attributed to respiratory failure secondary to central nervous system depression and to cardiac arrhythmias. Animal studies reveal that arrhythmias may result from sensitization of the heart to epinephrine. Hypoxia may exacerbate the situation. Therefore, acute lethal exposure levels may be lower in individuals exposed during physical exertion. Physical exertion also may decrease the acute lethal exposure level by increasing the respiratory rate and lung perfusion rate, thereby increasing the systemic absorption of 1,1,1-trichloroethane.

Very little is known about the lethality of ingested 1,1,1-trichloroethane in humans. In one case of acute oral exposure, accidental ingestion of 600 mg/kg of 1,1,1-trichloroethane was not fatal. Animal studies suggest that even higher acute oral doses may not cause death.

Neurological Effects. Neurological effects are the preeminent signs of acute inhalation exposure to 1,1,1-trichloroethane in humans. The intoxicating effects of the inhaled chemical create a potential for its abuse. The severity of central nervous system depressant effects in humans during acute inhalation exposure increases as the exposure duration and level are increased. Impaired performance of psychophysiological function tests has been observed in individuals exposed to moderate concentrations (≥175 ppm). The Mackay et al. study served as the basis for derivation of the acute-duration inhalation minimal risk level (MRL). Dizziness, lightheadedness, and loss of coordination are caused by exposure to higher concentrations (>500 ppm). General anesthesia occurs at high levels (≥10,000 ppm). These effects subside rapidly after exposure. One report suggested that impaired memory and deficits in balance were persistent effects in a group of workers after chronic exposure to moderate to high levels of 1,1,1-trichloroethane.

Animals are useful models for examining the neurological effects of exposure to 1,1,1-trichloroethane. As in humans, central nervous system depression is the predominant effect of inhaled 1,1,1-trichloro-

ethane. Signs include ataxia, unconsciousness, and death at increasing concentrations. No evidence of gross or histological damage was found in the brains of most exposed animals, although some evidence of potential for cellular damage was indicated by reports of increased levels of glial fibrillary acid protein and decreased DNA content in the brain of gerbils after repeated exposure to low levels of the chemical. The Rosengren et al. study served as the basis for the intermediate-duration inhalation MRL. Alterations of brain metabolism also were observed in exposed animals. Behavioral changes, including impaired performance of neurobehavioral tests and increased motor activity, have been widely reported; however, the sites of action and biochemical mechanisms of neurotoxicity have not been identified. Neurophysiological changes also have been reported. These latter observations were made at a relatively high exposure level (4,000 ppm).

Little information was located regarding neurological effects in humans or animals after oral or dermal exposure to 1,1,1-trichloroethane. Existing data indicate that a single oral exposure to a dose of approximately 600 mg/kg did not produce overt signs of neurotoxicity. It is assumed, however, that sufficiently high doses of 1,1,1-trichloroethane administered orally or dermally will result in neurological effects. Oral exposure to 1,1,1-trichloroethane produced neurophysiological changes in rats given moderate doses (700 mg/kg/day) and gross neurobehavioral changes (hyperexcitability and narcosis) in rats given high doses (≥2,500 mg/kg/day). No neurological effects were observed in the offspring of rats treated by gavage during gestation and lactation with up to 750 mg 1,1,1-trichloroethane/kg/day (see Developmental Effects). No clinical signs of neurotoxicity were seen in rats and mice receiving 1,1,1-trichloroethane in the diet at concentrations as high as 80,000 ppm (doses as high as 4,800 and 5,000 mg/kg/day in males and females, respectively) for 13 weeks.

Cardiovascular Effects. 1,1,1-Trichloroethane can lower blood pressure (mildly to severely) in humans and can induce transient myocardial injury. Such effects, however, are likely only after exposure to very high concentrations of 1,1,1-trichloroethane vapor. Chronic exposure of workers to levels ≤250 ppm did not affect blood pressure, heart rate, or electrocardiogram results in humans. Reduced blood pressure accompanies exposure to anesthetic concentrations of 1,1,1-trichloroethane vapor (10,000–26,000 ppm). The effects are not permanent and subside shortly after exposure. The hypotensive mechanism has been studied in animals and appears to involve cardiac depression and peripheral vasodilation.

Human deaths following 1,1,1-trichloroethane inhalation are often attributed to cardiac arrhythmias. Such conclusions are based on animal studies in which arrhythmias have been produced during or immediately following acute inhalation exposure to 1,1,1-trichloroethane. The mechanism for the arrhythmias apparently involves sensitization of the heart to endogenous epinephrine. The exposure level at which cardiac sensitization occurs in humans is not known, but in animals, concentrations as low as 5,000 ppm are effective after only 10 minutes of inhalation. Physical exertion, stress, or any other stimulus of epinephrine release from the adrenal medulla may render an individual more vulnerable to 1,1,1-trichloroethane. Hypoxia may further increase a subject's susceptibility.

Hepatic Effects. 1,1,1-Trichloroethane may be a mild hepatotoxin in humans, although the evidence is not conclusive. Increased levels of serum bilirubin, lactate dehydrogenase (LDH), alkaline phosphatase, and serum glutamic oxaloacetic transaminase (SGOT), all suggestive of liver injury, have been reported in humans exposed to high levels of 1,1,1-trichloroethane by inhalation or ingestion. Elevated serum LDH, gamma-glutamyl transpeptidase (GGT), SGOT, and glutamic pyruvic transaminase (SGPT), and pathologic signs of progressive liver disease were noted in a patient who was occupationally exposed to 1,1,1-trichloroethane for several years. Removal of the patient from exposure resulted in improvement of the impaired liver function. Mild hepatic changes have also been noted in liver biopsies of exposed individuals and at autopsy in individuals who died after acute inhalation exposure to high concentrations of 1,1,1-trichloroethane. Animal studies indicate that exposure to relatively high 1,1,1-trichloroethane concentrations in air (≥1,000 ppm) or high oral doses (≥1,334 mg/kg) are required to produce liver injury. Effects observed in animals include necrosis, fatty change, increased liver weight, and changes in liver and serum enzyme levels. These effects are reversible and subside after termination of exposure (in the case of necrosis, hepatocytes in the proximity of the killed cells proliferate and replace them).

Developmental Effects. Developmental effects in humans exposed to 1,1,1-trichloroethane have not been observed. Epidemiology studies found no relationship between adverse pregnancy outcomes and maternal exposure to 1,1,1-trichloroethane. Minor embryotoxic effects were observed in rats and rabbits after inhalation exposure to high concentrations of 1,1,1-trichloroethane. Effects included decreased fetal weights, increased minor soft tissue and skeletal anomalies, and delayed ossification. Exposure of pregnant mice to 1,1,1-trichloroethane at a concentration of 2,000 ppm for 17 hours/day on gestation days 12–17 resulted in significantly reduced postnatal pup weights, overt developmental delays (pinnae detachment, incisor eruption, eye opening), and impaired performance in behavioral tests (righting reflex,

forelimb grip strength, negative geotaxis, inverted screen climbing). In a similar study of pregnant rats that were exposed to 7,000 ppm of 1,1,1-trichloroethane 3 times/day for 60 minutes on gestation days 13–19, two of nine litters were completely resorbed and significant increases in gestation length were noted. Developmental effects included increased mortality at birth, decreased litter weight, and significant deficits in coordination, muscle strength, and spontaneous motor activity. The developmental defects reported in three of these studies may have been associated with significant maternal toxicity. Neither an inhalation study using a lower, although still high, concentration nor drinking water studies revealed any developmental effects. Furthermore, a comprehensive study in which pregnant rats were gavaged with 1,1,1-trichloroethane during gestation and lactation found no neurobehavioral alterations in the pups tested up to 2 months of age. Overall, 1,1,1-trichloroethane does not appear to be a significant developmental toxicant in animals. However, in view of the known neurological effects of 1,1,1-trichloroethane in humans and animals, additional developmental studies that examine neurological end points would be an important component of a complete investigation of 1,1,1-trichloroethane's potential developmental toxicity in humans.

Cancer. A relationship between exposure to 1,1,1-trichloroethane and cancer in humans has not been established. Among animals, no effects were found in a well-designed inhalation study at exposure levels ≤1,500 ppm. The results of an oral study indicate that 1,1,1-trichloroethane may have increased the occurrence of immunoblastic lymphosarcoma in rats; however, the biological and statistical significance of these results are questionable because of the study design limitations. The results of another oral (gavage) cancer bioassay were negative, but high early mortality in treated animals in this study made these results questionable.

Information is also limited on the role of 1,1,1-trichloroethane metabolites in the parent compound's toxicity. Reactive metabolites are important in the carcinogenicity of other chloroethanes (i.e., 1,1,2,2-tetrachloroethane). Binding to DNA, which is correlated with carcinogenicity in chlorinated ethanes, was weak in an *in vivo* test. Even weak binding, however, indicates the potential to interact with DNA. Cell biotransformation tests were positive for this chemical. The results of these assays may have been confounded by the presence of stabilizing agents, however. Two of the common stabilizing additives in commercial formulations of 1,1,1-trichloroethane are 1,2-epoxybutane (butylene oxide) and 1,4-dioxane (diethylene dioxide). Both stabilizers have been identified as animal carcinogens. At this time, it does not appear that 1,1,1-trichloroethane exposure poses a clear cancer risk in animals; however, as discussed above, the limitations of the available studies prevent a definitive assessment of the risk of

cancer in humans exposed to the compound. Related to potential exposures near NPL hazardous waste sites, the risk appears to be of little significance.

2.3 MINIMAL RISK LEVELS

Inhalation MRLs

- An MRL of 2 ppm has been derived for acute-duration inhalation exposure (14 days or less) to 1,1,1-trichloroethane.

The acute-duration inhalation MRL is based on a lowest-observed-adverse-effect level (LOAEL) of 175 ppm for reduced performance of psychomotor tests in a human study by Mackay et al. (1987). Individuals exposed to 175 or 350 ppm of 1,1,1-trichloroethane for 3.5 hours demonstrated impaired performance of psychomotor tests. The derivation of this MRL is supported by results of other human studies. Gamberale and Hultengren (1973) found psychophysiological test performance deficits in exposed individuals, although at a higher concentration than the LOAEL of 175 ppm identified by Mackay et al. (1987). Muttray et al. (1999, 2000) found EEG changes consistent with increased drowsiness and slight irritant nasal responses in volunteers exposed to 200 ppm. Numerous studies described behavioral and neurophysiological effects in animals.

Although the LOAEL of 175 ppm in the critical study of Mackay et al. (1987) was associated with only a 3.5-hour exposure period, the acute-duration inhalation MRL is intended to be protective of a continuous acute-duration exposure. Data reported by Nolan et al. (1984) and Mackay et al. (1987) indicate that blood levels of 1,1,1-trichloroethane approach steady state during 2 hours of continuous inhalation exposure in humans. Neurobehavioral performance was correlated with 1,1,1-trichloroethane blood levels and there was little additional change in most measures of neurobehavioral performance as exposure duration increased from 2 to 3 hours (Mackay et al. 1987). Therefore, the LOAEL of 175 ppm was not adjusted for exposure duration.

- An MRL of 0.7 ppm has been derived for intermediate-duration inhalation exposure (15–364 days) to 1,1,1-trichloroethane.

The intermediate-duration inhalation MRL is based on a no-observed-adverse-effect level (NOAEL) of 70 ppm derived from the study by Rosengren et al. (1985), which found evidence of astrogliosis

(increased glial fibrillary acid protein levels) in the brains of gerbils exposed to 210 or 1,000 ppm, but not 70 ppm, of 1,1,1-trichloroethane continuously for 3 months. Choice of a neurological end point for derivation of the MRL is supported by numerous studies in humans and animals showing neurological effects to be the critical end point for 1,1,1-trichloroethane.

A chronic-duration inhalation MRL was not derived because suitable studies including tests for subtle neurological effects were not available.

Oral MRLs

An acute-duration oral MRL was not derived for 1,1,1-trichloroethane due to the lack of adequate information. Acute-duration oral exposure in humans is limited to a single account of an accidental exposure. Comprehensive acute-duration oral toxicity studies in animals were not located and available studies did not clearly establish sensitive targets and dose-response relationships.

- An MRL of 20 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to 1,1,1-trichloroethane.

The intermediate-duration oral MRL is based on a NOAEL for body weight effects in mice (NTP 2000). Groups of male and female B6C3F1 mice (10 per group) were administered microencapsulated 1,1,1-trichloroethane in the diet at concentrations of 0, 5,000, 10,000, 20,000, 40,000, or 80,000 ppm, 7 days/week for 13 weeks. Untreated control groups of 10 males and 10 females were included in the study. Respective average doses of 1,1,1-trichloroethane calculated by the researchers were 850, 1,770, 3,500, 7,370, and 15,000 mg/kg/day in male mice; and 1,340, 2,820, 5,600, 11,125, and 22,900 mg/kg/day in female mice. Clinical signs and body weights were recorded weekly. Food consumption was determined every 3–4 days. Vaginal cytology and sperm motility evaluations were performed on all mice in the vehicle control and the three highest dose groups of mice. At necropsy, all mice were subjected to gross pathological examinations, and the heart, lungs, thymus, liver, right kidney, and right testis were weighed. Mice in untreated and vehicle control and high-dose groups were subjected to complete histopathologic examinations.

There were no exposure-related deaths. Food consumption was slightly increased in 1,1,1-trichloroethane-treated groups, relative to untreated and vehicle controls. However, the final mean body weights of all groups of 1,1,1-trichloroethane-treated male mice were significantly lower (9, 9, 12, 10, and 15%

lower in the 5,000-, 10,000-, 20,000-, 40,000-, and 80,000-ppm male groups, respectively) than that of the untreated controls. Mean body weight gain in all treatment groups was also significantly less than that of the untreated controls (12, 16, 23, 22, and 33% lower in 5,000-, 10,000-, 20,000-, 40,000-, and 80,000-ppm groups, respectively). There were no indications of treatment-related clinical or histopathological effects. A treatment-related decrease in body weight (or body weight gain) of 10% or more (relative to controls) may be considered to represent an adverse effect. The choice of 1,1,1-trichloroethane-induced body weight changes as the critical effect is supported by results of other subchronic- and chronic-duration oral and inhalation animal studies in which body weight effects were reported, either in the absence of other signs of toxicity (Adams et al. 1950; Bruckner et al. 2001; Prendergast et al. 1967) or at doses causing minimal liver lesions (Calhoun et al. 1981; Quast et al. 1978, 1988).

A total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) was applied to the NOAEL of 1,770 mg/kg/day for body weight effects in male mice administered 1,1,1-trichloroethane in the diet for 13 weeks.

Results of another intermediate-duration oral animal study were evaluated for the purpose of deriving an intermediate-duration oral MRL for 1,1,1-trichloroethane. Bruckner et al. (2001) reported a frank effect level (FEL) of 2,500 mg/kg (1,786 mg/kg/day when adjusted for exposure 5 days/week) for gross central nervous system depression and death in rats exposed by gavage. Investigation of systemic end points was limited to the liver; only mild hepatic changes were found and only at lethal doses. Sensitive neurological endpoints were not monitored. NTP (2000) observed no gross central nervous system effects or deaths at doses up to about 5,000 mg/kg/day in rats or 23,000 mg/kg/day in mice. The differences in the findings of the Bruckner et al. (2001) and NTP (2000) studies can be attributed to the bolus dosing employed by Bruckner et al. (2001). In comparison to relatively steady intake throughout the day in the diet, bolus dosing will produce much higher peak blood levels as the entire daily dose is rapidly absorbed. The gross central nervous system effects and mortality observed by Bruckner et al. (2001) are likely a reflection of the high peak blood levels by this mode of administration. Such bolus oral exposure is not considered relevant to longer-term or chronic exposure scenarios in humans. Therefore, the results of Bruckner et al. (2001) were not used as the basis for derivation of an intermediate-duration oral MRL for 1,1,1-trichloroethane.

A chronic-duration oral MRL was not derived for 1,1,1-trichloroethane. No relevant human data were located. Chronic-duration oral animal studies were designed as cancer bioassays and included only limited investigation of noncancer endpoints (Maltoni et al. 1986; NCI 1977).

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 1,1,1-trichloroethane. 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.

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for 1,1,1-trichloroethane. 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.

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.

3.2.1 Inhalation Exposure

3.2.1.1 Death

1,1,1-Trichloroethane is one of many solvents intentionally inhaled by some people to alter mood or consciousness. Solvent abuse of this type is associated with "sudden sniffing death" syndrome. In a survey of sudden sniffing deaths across the United States in the 1960s, 29 of the 110 deaths in the survey were attributed to inhalation of 1,1,1-trichloroethane (Bass 1970). Case reports of individuals who died following intentional inhalation of 1,1,1-trichloroethane are readily available (D'Costa and Gunasekera 1990; Droz et al. 1982; Guberan et al. 1976; Hall and Hine 1966; MacDougall et al. 1987; Ranson and Berry 1986; Travers 1974; Winek et al. 1997). 1,1,1-Trichloroethane is a widely used industrial solvent. Although mortality due to accidental exposure from its use as a solvent is not common, a number of cases have been reported (Caplan et al. 1976; Jones and Winter 1983; McCarthy and Jones 1983; Commission of the European Communities 1981; Northfield 1981; Silverstein 1983; Stahl et al. 1969; Sullivan 1994).

Data from case reports and surveys are useful, but concomitant exposure to other chemicals cannot be ruled out, and exposure concentrations and durations are rarely known. Although the actual levels of exposure that produced death are not known for any of these cases, some investigators used simulations to estimate the fatal exposure concentrations. Droz et al. (1982) performed detailed simulations of two fatalities from intentional 1,1,1-trichloroethane inhalation. The lethal concentration of 1,1,1-trichloroethane was estimated to be between 6,000 and 14,000 ppm in one case and between 10,000 and 20,000 ppm in the other. Simulation of the circumstances of deaths of two people exposed while using 1,1,1-trichloroethane as a solvent showed that concentrations ≤6,400 ppm may have been generated in one case (Jones and Winter 1983) and concentrations ≤9,000 ppm may have been generated in the other (Silverstein 1983). Northfield (1981) reported a case in which a worker, whose death was attributed to respiratory failure, may have been exposed to 1,1,1-trichloroethane concentrations of 6,000 ppm or higher, depending on distance from the source.

Human death following acute exposure to high 1,1,1-trichloroethane concentrations is usually attributed to either depression of the central nervous system, which results in respiratory arrest (Hall and Hine 1966; Jones and Winter 1983; Stahl et al. 1969; Winek et al. 1997), or sensitization of the heart to epinephrine, which results in severe cardiac arrhythmias (Guberan et al. 1976; MacDougall et al. 1987; Travers 1974). The occurrence of death during physical exertion following inhalation of 1,1,1-trichloroethane (Ranson and Berry 1986) or a mixture of 1,1,1-trichloroethane and trichloroethylene (King et al. 1985; Troutman

1988) is consistent with the possibility that cardiac sensitization to epinephrine caused death in these cases. It should be noted that anoxia or hypoxia, which are present to some extent during physical exertion, exacerbate the cardiac arrhythmias caused by sensitization of the myocardium to catecholamines (Reinhardt et al. 1971).

Studies of animal mortality following acute inhalation exposure to 1,1,1-trichloroethane are numerous. Median lethal concentrations (LC_{50} values) have been calculated for rats and mice. For rats, LC_{50} values from 10,305 to 38,000 ppm were reported (Adams et al. 1950; Bonnet et al. 1980; Clark and Tinston 1982). For mice, reported LC_{50} values ranged from 3,911 to 22,241 ppm (Gradiski et al. 1978; Horiguchi and Horiguchi 1971; Moser and Balster 1985; Woolverton and Balster 1981). Much of the variation in these data can be attributed to differences in the exposure duration (higher LC_{50} values were generally obtained in studies with short exposure periods). In studies of the same duration, rats (6-hour LC_{50}=10,305 ppm) were somewhat more susceptible to 1,1,1-trichloroethane than mice (6-hour LC_{50}=13,414 ppm) (Bonnet et al. 1980; Gradiski et al. 1978). An alternative way to study lethality is to expose animals to a given concentration of vapor and record the time required to kill half of the animals (LT_{50}). The LT_{50} was 180 minutes in rats exposed to 18,000 ppm of 1,1,1-trichloroethane (Adams et al. 1950) and 595 minutes in mice exposed to 13,500 ppm (Gehring 1968). Deaths of animals exposed to 1,1,1-trichloroethane were usually attributed to either respiratory or cardiac failure (Adams et al. 1950; Clark and Tinston 1982; Krantz et al. 1959). Most deaths occurred during exposure. Animals that survived the exposure period usually recovered rapidly and appeared normal within 10–15 minutes (Adams et al. 1950; Clark and Tinston 1982).

1,1,1-Trichloroethane did not increase mortality in longer-term studies in which animals were exposed to lower exposure concentrations than the acute studies. No effects on survival were observed in intermediate-duration studies in which animals of several species were exposed to concentrations ≤5,000 ppm (Adams et al. 1950; Calhoun et al. 1981; Prendergast et al. 1967; Rosengren et al. 1985) or chronic-duration studies in which rats and mice were exposed to concentrations ≤1,750 ppm (Quast et al. 1978, 1988).

Reliable acute LC_{50} values for death in each species are recorded in Table 3-1 and plotted in Figure 3-1. Acute exposure to high concentrations of 1,1,1-trichloroethane can be lethal to humans and animals. The cause of death is usually either respiratory or cardiac failure. Limited human data and studies in animals

Table 3-1 Levels of Significant Exposure to 1,1,1-Trichloroethane - Inhalation

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
	ACUTE EXPOSURE						
	Death						
1	Rat (Wistar)	Once 6-420 min				14250 (LC50 - 7 hr)	Adams et al. 1950
2	Rat (Sprague-Dawley)	1 d 6 hr/d				10305 M (LC50 - 6 hr)	Bonnet et al. 1980
3	Rat (Alderley Park)	1 d 10-15 min/d				38000 (LC50 - 15 min)	Clark and Tinston 1982
4	Mouse (OF1)	1 d 6 hr/d				13414 F (LC50 - 6 hr)	Gradiski et al. 1978
5	Mouse (NA2)	1 d 2 hr/d				3911 M (LC50 - 2 hr)	Horiguchi and Horiuchi 1971
6	Mouse (CD-1)	1 d 10-60 min/d				18358 M (LC50 - 60 min)	Moser and Balster 1985
7	Mouse (CD-1)	1 d 30 min/d				22241 M (LC50 - 30 min)	Woolverton and Balster 1981

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
	Systemic						
8	Human	1 d up to 2 hr/d	Resp	10000			Dornette and Jones 1960
			Cardio		10000 (5-10 mm Hg reduction in blood pressure)		
			Hepatic	10000			
9	Human	1 d 30 min/d	Cardio	550 M			Gamberale and Hultengren 1973
10	Human	Once 4 hr	Resp		200 M (nasal irritation)		Muttray et al. 1999
11	Human	1 d 15-186 min/d	Resp		1900 M (throat irritation)		Stewart et al. 1961
			Hepatic	2650 M			
			Renal	2650 M			

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
12	Human	5 d 1-7.5 hr/d	Resp	500			Stewart et al. 1975
			Hemato	500			
			Hepatic	500			
			Renal	500			
13	Human	1 d 5-450 min/d	Resp	506			Torkelson et al. 1958
			Cardio	920			
			Hemato	920			
			Hepatic	920			
			Renal	920			
14	Rat (Wistar)	Once 6-420 min	Bd Wt	30000			Adams et al. 1950

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
15	Rat (Wistar)	Once 6-420 min	Resp	18000 M			Adams et al. 1950
			Cardio	18000 M			
			Hepatic		8000 M (increased liver weight, mild fatty change)		
			Renal	18000 M			
			Bd Wt	18000 M			
16	Rat (NS)	1 d 2 hr/d	Hepatic	13070 M			Carlson 1973

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
17	Rat (Sprague-Dawley)	1 d 2 hr/d	Resp	15000 M			Cornish and Adefuin 1966
			Hepatic	15000 M			
			Renal	15000 M			
			Endocr	15000 M			
			Bd Wt	15000 M			
18	Rat (Sprague-Dawley)	1 d 24 hr/d	Hepatic	2500 M			Fuller et al. 1970
19	Rat (Wistar)	10 d 24 hr/d	Hemato	800 M			Koizumi et al. 1983
			Hepatic	800 M			
20	Rat (Sprague-Dawley)	5 d 6 hr/d	Hepatic	500 M			Savolainen et al. 1977

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL			Reference Chemical Form
					Less Serious (ppm)	Serious (ppm)		
21	Mouse (CFW Swiss)	4 d 24 hr/d	Bd Wt	2000 M		4000 M	(26% reduction in body weight)	Evans and Balster 1993
22	Mouse (Swiss Webster)	1 d 10-780 min/d	Hepatic	13500 F				Gehring 1968
23	Mouse (CD-1)	Gd 12-17 60 min/exposure 3 exposures/d	Bd Wt	8000 F				Jones et al. 1996
24	Mouse (Swiss albino)	1-6 d 4-24 hr/d	Hepatic	6000 M				Lal and Shah 1970
25	Dog (Beagle)	1 d 5 min/d	Cardio			7500	(EC50 for cardiac sensitization)	Clark and Tinston 1973
26	Dog (Beagle)	1 d 15 min/d	Cardio	10000				Egle et al. 1976

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
27	Dog (NS)	1 d 5 min/d	Resp	25000			Herd et al. 1974
			Cardio			8000 (50 mm Hg reduction in mean blood pressure)	
			Hepatic	25000			
28	Dog (Beagle)	1 d 10 min/d	Cardio	2500 M		5000 M (cardiac sensitization)	Reinhardt et al. 1973
29	Rabbit (New Zealand)	1 d 7.5-60 min/d	Cardio			5600 M (cardiac sensitization)	Carlson 1981
	Immuno/ Lymphoret						
30	Rat (Sprague-Dawley)	1 d 2 hr/d		15000 M			Cornish and Adefuin 1966
31	Mouse (CD-1)	1 d 3 hr/d		350 F			Aranyi et al. 1986

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

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
	Neurological						
32	Human	1 d up to 2 hr/d				10000 (anesthesia)	Dornette and Jones 1960
33	Human	1 d 30 min/d		250 M	350 M (increased reaction time, decreased perceptual speed and manual dexterity)		Gamberale and Hultengren 1973
34	Human	Once 5 hr		200 M			Laine et al. 1996
35	Human	1 d 3.5 hr/d			175 M[b] (decreased psychomotor performance)		Mackay et al. 1987
36	Human	Once 4 hr			200 M (increased drowsiness)		Muttray et al. 2000
37	Human	1 d 8hr/d		450 M			Salvini et al. 1971

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
38	Human	1 d 4hr/d		400 M			Savolainen et al. 1981
39	Human	1 d 15-186 min/d		496 M		900 M (lightheadedness)	Stewart et al. 1961
40	Human	5 d 6.5-7 hr/d				500 M (impaired balance)	Stewart et al. 1969
41	Human	5 d 1-7.5 hr/d		350	500 (altered EEG)		Stewart et al. 1975
42	Human	1 d 5-450 min/d				920 (ataxia)	Torkelson et al. 1958
43	Monkey (Baboon)	1 d 4 hr/d		1400 M	1800 M (increased response time in match to sample task)		Geller et al. 1982

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
44	Rat (Wistar)	Once 6-420 min				5000 (narcosis)	Adams et al. 1950
45	Rat (Sprague-Dawley)	1 d 6 hr/d				10000 M (all somnolent)	Bonnet et al. 1980
46	Rat (Alderley Park)	1 d 10-15 min/d				5000 (EC50 for ataxia)	Clark and Tinston 1982
47	Rat (Wistar)	1 d 5-60 min/d			8000 M (increased brain lactate and pyruvate)		Folbergrova et al. 1984
48	Rat (Fischer 344)	4 d 6 hr/d			4000 (increased motor activity)		Halogenated Solvents Industry Alliance 1991
49	Rat (Fischer 344)	4 d 6 hr/d			1000 F (altered EEG, FEP, and SEP)		Halogenated Solvents Industry Alliance 1991
50	Rat (Wistar)	1 d 0.5-2 hr/d		3500 M	6000 M (dizzness, decrease local cerebral glucose consumption)	7800 M (ataxia)	Hougaard et al. 1984

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

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
51	Rat (Charles River-CD)	1 d 0.5-4 hr/d		1750 M		3080 M (impaired reflexes)	Mullin and Krivanek 1982
52	Rat (Sprague-Dawley)	40 or 100 min			5000 M (reduced cGMP in the brain)		You and Dallas 2000
53	Mouse (CD-1)	1 d 20 min/d				2836 M (EC50 for effect on operant behavior)	Balster et al. 1982
54	Mouse (CFW)	30 min			1250 M (increased motor activity)		Bowen and Balster 1996
55	Mouse (albino)	30 min 2x/wk		2000 M	4000 M (increased motor activity)		Bowen and Balster 1998
56	Mouse (albino)	30 min 2x/wk		2000 M	4000 M (altered schedule-controlled behavior)		Bowen and Balster 1998

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
57	Mouse (albino)	Once 30 min			2500 M (increased anxiety)		Bowen et al. 1996a
58	Mouse (albino)	20 min 1x		4000 M		8000 M (significantly impaired righting reflex)	Bowen et al. 1996b 1,1,1-trichloroethane
59	Mouse (Swiss OF1)	1 d 4 hr/d				6644 M (EC50 for increased seizure threshold)	De Ceaurriz et al. 1981
60	Mouse (Swiss OF1)	1 d 4 hr/d				2064 M (altered swimming behavior)	De Ceaurriz et al. 1983
61	Mouse (CFW Swiss)	4 d 24 hr/d				500 M (decreased threshold to convulsions upon withdrawal)	Evans and Balster 1993
62	Mouse (Swiss Webster)	1 d 10-780 min/d				13500 F (unconsciousness)	Gehring 1968

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
63	Mouse (CD-1)	Gd 12-17 60 min/exposure 3 exposures/d				8000 F (mild tremors and gait abnormalities in dams)	Jones et al. 1996
64	Mouse (NMRI)	1 d 1hr/d		1300 M	2000 M (increased motor activity)		Kjellstrand et al. 1985a
65	Mouse (CD-1)	1 d 10-60 min/d				5674 M (EC50 for impaired screen climbing ability)	Moser and Balster 1985
66	Mouse (CD-1)	1 d 30 min/d				7129 M (EC50 for reduced fixed interval response rate)	Moser and Balster 1986
67	Mouse (NS)	1 d 4 hr/d		500 M	1000 M (increased cAMP in brain)		Nilsson 1986a
68	Mouse (NS)	1 d 4 hr/d		50 M	100 M (reduced cGMP in brain)		Nilsson 1986b

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
69	Mouse (Swiss-Webster)	Once 30 min		4000	8000 (increased anxiety)		Páez-Martínez et al. 2003 1,1,1-trichloroethane
70	Mouse (CD-1)	1 d 20 min/d				2876 M (EC50 for effect on ability to discriminate from pentobarbital)	Rees et al. 1987a
71	Mouse (CD-1)	1 d 20 min/d				850 M (EC50 for effect on ability to discriminate from ethanol)	Rees et al. 1987b
72	Mouse (CD-1)	1 d 30 min/d				5173 M (EC50 for impaired screen climbing ability)	Woolverton and Balster 1981
73	Mouse (CD-1)	40 or 100 min			5000 M (reduced cGMP in the brain)		You and Dallas 2000
74	Dog (Beagle)	1 d 15 min/d		10000			Egle et al. 1976

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)		LOAEL Serious (ppm)		Reference Chemical Form
	Reproductive								
75	Rat (NS)	Once 6-420 min		18000 M					Adams et al. 1950
	Developmental								
76	Rat (CD)	Gd 6-15 4 hr/d		3000 F	6000 F	(decreased female fetal weight, delayed ossification)			BRRC 1987a
77	Rat (Sprague-Dawley)	Gd 6-15 7 hr/d		875 F					Schwetz et al. 1975
78	Mouse (CD-1)	Gd 12-17 17 hr/d					2000	(delayed development and impaired motor skills)	Jones et al. 1996
79	Mouse (CD-1)	Gd 12-17 17 hr/d	Bd Wt		2000	(18% decreased litter weight)			Jones et al. 1996
80	Mouse (CD-1)	Gd 12-17 60 min/exposure 3 exposures/d			8000	(reduced litter and postnatal pup weight)	8000	(delayed development, impaired performance in behavioral tests)	Jones et al. 1996

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
81	Mouse (CD-1)	Gd 12-17 17 hr/d			2000 (18% decreased litter weight)		Jones et al. 1996 1,1,1-trichloroethane
82	Mouse (Swiss Webster)	Gd 6-15 7 hr/d		875 F			Schwetz et al. 1975
83	Rabbit (New Zealand)	Gd 6-18 6 hr/d		3000 F	6000 F (extra rib)		BRRC 1987b
	INTERMEDIATE EXPOSURE						
	Systemic						
84	Monkey (NS)	14 wk 7 d/wk 24 hr/d	Resp	1000			MacEwen and Vernot 1974
			Hemato	1000			
			Hepatic	1000			
			Renal	1000			

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
85	Monkey (Squirrel)	6 wk 5 d/wk 8 hr/d	Resp	2210			Prendergast et al. 1967
			Cardio	2210			
			Hepatic	2210			
			Renal	2210			
			Bd Wt	2210			
86	Rat (NS)	44 d 5 d/wk 7 hr/d	Resp	5000			Adams et al. 1950
			Cardio	5000			
			Hepatic	5000			
			Renal	5000			
			Bd Wt	5000			

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)		LOAEL Serious (ppm)	Reference Chemical Form
87	Rat (CDF)	90 d 5 d/wk 6 hr/d	Resp	1000	2000	(mild nasal epithelial degeneration)		Calhoun et al. 1981
			Cardio	2000				
			Gastro	2000				
			Hemato	2000				
			Musc/skel	2000				
			Hepatic	1000	2000	(reduced glycogen, fatty change)		
			Renal	2000				
			Dermal	2000				
			Ocular	2000				
			Bd Wt	2000				

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
88	Rat (NS)	14 wk 24 hr/d	Resp	1000			MacEwen and Vernot 1974
			Hepatic	1000			
			Renal	1000			
			Bd Wt	1000			
89	Rat (Sprague-Dawley)	6 wk 5 d/wk 8 hr/d	Resp	2210			Prendergast et al. 1967
			Cardio	2210			
			Hemato	2210			
			Hepatic	2210			
			Renal	2210			
			Bd Wt	2210			

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

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
90	Rat (Sprague-Dawley)	4 wk 5 d/wk 6 hr/d	Hepatic	820 M			Toftgard et al. 1981
			Bd Wt	820 M			
91	Rat (NS)	3 mo 5 d/wk 3-60 min/d	Hepatic	10000 M			Torkelson et al. 1958
			Renal	10000 M			
			Bd Wt	10000 M			
92	Rat (Sprague-Dawley)	15 wk 5 d/wk 5-6 hr/d	Resp	1100 F			Truffert et al. 1977
			Hemato	1100 F			
			Hepatic	1100 F			
			Renal	1100 F			
			Bd Wt	1100 F			

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)		LOAEL Serious (ppm)	Reference Chemical Form
93	Mouse (B6C3F1)	90 d 5 d/wk 6 hr/d	Resp	1000	2000	(mild nasal epithelial degeneration)		Calhoun et al. 1981
			Cardio	2000				
			Gastro	2000				
			Hemato	2000				
			Musc/skel	2000				
			Hepatic	1000	2000	(fatty change)		
			Renal	2000				
			Dermal	2000				
			Ocular	2000				
			Bd Wt	2000				
94	Mouse (CF1)	14 wk 24 hr/d	Hepatic	250 M	1000 M	(fatty change, necrosis)		McNutt et al. 1975

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
95	Gn Pig (NS)	45 d 5 d/wk 7 hr/d	Resp	5000			Adams et al. 1950
			Hepatic		5000 (fatty change)		
			Renal	5000			
			Bd Wt			5000 (over 20% decrease body weight gain)	
96	Gn Pig (NS)	29 d 5 d/wk 7 hr/d	Resp	3000			Adams et al. 1950
			Cardio	3000			
			Hepatic		3000 (fatty change)		
			Renal	3000			
			Bd Wt			3000 (over 20% reduction in body weight gain)	

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

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
97	Gn Pig (NS)	93 d 5 d/wk 7 hr/d	Resp	650			Adams et al. 1950
			Cardio	650			
			Hepatic	650			
			Renal	650			
			Bd Wt		650 (body weight gain reduced 18-35%)		
98	Gn Pig (Hartley)	6 wk 5 d/wk 8 hr/d	Resp	2210			Prendergast et al. 1967
			Cardio	2210			
			Hemato	2210			
			Hepatic	2210			
			Renal	2210			
			Bd Wt	2210			

[a]

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

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
99	Gn Pig (NS)	3 mo 5 d/wk 3-180 min/d	Resp		1000 F (lung irritation)		Torkelson et al. 1958
			Hepatic		1000 F (fatty change)		
			Renal	2000 F			
			Bd Wt	2000 F			
100	Dog (NS)	14 wk 24 hr/d	Gastro	1000			MacEwen and Vernot 1974
			Hemato	1000			
			Hepatic	1000			
			Renal	1000			

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)		Reference Chemical Form
101	Dog (Beagle)	90 d 24 hr/d	Resp	380				Prendergast et al. 1967
			Cardio	380				
			Hemato	380				
			Hepatic	380				
			Renal	380				
			Bd Wt	140		380	(body weight gain reduced 51%)	

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

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
102	Dog (Beagle)	6 wk 5 d/wk 8 hr/d	Resp	2210			Prendergast et al. 1967
			Cardio	2210			
			Hemato	2210			
			Hepatic	2210			
			Renal	2210			
			Bd Wt		2210 (body weight gain reduced >12%)		
103	Rabbit (NS)	44 d 5 d/wk 7 hr/d	Resp	5000 F			Adams et al. 1950
			Hepatic	5000 F			
			Renal	5000 F			
			Bd Wt		5000 F (slight decrease in body weight gain)		

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

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)		Reference Chemical Form
104	Rabbit (New Zealand albino)	90 d 24 hr/d	Resp	380				Prendergast et al. 1967
			Cardio	380				
			Hemato	380				
			Hepatic	380				
			Renal	380				
			Bd Wt	140		380	(66% reduction in body weight gain)	

[a]

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

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)		Reference Chemical Form
105	Rabbit (New Zealand albino)	6 wk 5 d/wk 8 hr/d	Resp	2210				Prendergast et al. 1967
			Cardio	2210				
			Hemato	2210				
			Hepatic	2210				
			Renal	2210				
			Bd Wt			2210	(over 34% reduction in body weight gain)	

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

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
106	Rabbit (NS)	6 mo 5 d/wk 7 hr/d	Resp	500			Torkelson et al. 1958
			Cardio	500			
			Hemato	500			
			Hepatic	500			
			Renal	500			
			Bd Wt	500			
107	Gerbil (Mongolian)	3 mo 24 hr/d	Bd Wt	1000			Rosengren et al. 1985
	Immuno/ Lymphoret						
108	Monkey (Squirrel)	6 wk 5 d/wk 8 hr/d		2210			Prendergast et al. 1967
109	Rat (Sprague-Dawley)	6 wk 5 d/wk 8 hr/d		2210			Prendergast et al. 1967

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

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
110	Mouse (B6C3F1)	90 d 5 d/wk 6 hr/d		2000			Calhoun et al. 1981
111	Gn Pig (NS)	45 d 5 d/wk 7 hr/d		5000			Adams et al. 1950
112	Dog (Beagle)	6 wk 5 d/wk 8 hr/d		2210			Prendergast et al. 1967
113	Rabbit (NS)	44 d 5 d/wk 7 hr/d		5000 F			Adams et al. 1950
	Neurological						
114	Monkey (Squirrel)	6 wk 5 d/wk 8 hr/d		2210			Prendergast et al. 1967
115	Rat (Fischer 344)	13 wk 5 d/wk 6 hr/d		630	2000 (decreased forelimb grip performance)		Mattsson et al. 1993
116	Rat (Sprague-Dawley)	6 wk 5 d/wk 8 hr/d		2210			Prendergast et al. 1967

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
117	Rat (NS)	3 mo 5 d/wk 3-60 min/d				10000 M (ataxia, narcosis)	Torkelson et al. 1958
118	Mouse (CD-1)	4 wk 4 d/wk 20 min/d			3300 M (EC50 for decreased response rate)		Moser et al. 1985
119	Gn Pig (Hartley)	6 wk 5 d/wk 8 hr/d		2210			Prendergast et al. 1967
120	Dog (Beagle)	6 wk 5 d/wk 8 hr/d		2210			Prendergast et al. 1967
121	Rabbit (New Zealand albino)	6 wk 5 d/wk 8 hr/d		2210			Prendergast et al. 1967
122	Gerbil (Mongolian)	3 mo 24 hr/d		70[c]		210 (increased GFA protein indicating astrogliosis)	Rosengren et al. 1985
	Reproductive						
123	Rat (NS)	44 d 5 d/wk 7 hr/d		5000 M			Adams et al. 1950

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
124	Mouse (B6C3F1)	90 d 5 d/wk 6 hr/d		2000			Calhoun et al. 1981
125	Gn Pig (NS)	45 d 5 d/wk 7 hr/d			5000 M (testicular degeneration)		Adams et al. 1950
126	Gn Pig (NS)	29 d 5 d/wk 7 hr/d		3000 M			Adams et al. 1950
127	Rabbit (NS)	6 mo 5 d/wk 7 hr/d		500 M			Torkelson et al. 1958
	Developmental						
128	Rat Long-Evans	premating:2 wk 5 d/wk 6 hr/d pregnancy:Gd 1-20 7 d/wk 6 hr/d			2100 F (delayed ossification, reduced clavicle)		York et al. 1982

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
	CHRONIC EXPOSURE						
	Systemic						
129	Human	up to 6 yr (occup)	Cardio	150			Kramer et al. 1978
			Hemato	150			
			Hepatic	150			
			Renal	150			
130	Rat (Fischer 344)	2 yr 5 d/wk 6 hr/d	Resp	1500			Quast et al. 1988
			Cardio	1500			
			Gastro	1500			
			Hemato	1500			
			Musc/skel	1500			
			Hepatic	500	1500	(mild liver histopathology)	
			Renal	1500			
			Bd Wt	1500 F			

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

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
131	Mouse (B6C3F1)	2 yr 5 d/wk 6 hr/d	Resp	1500			Quast et al. 1988
			Cardio	1500			
			Gastro	1500			
			Hemato	1500			
			Musc/skel	1500			
			Hepatic	1500			
			Renal	1500			
			Dermal	1500			
			Bd Wt	1500			
	Immuno/ Lymphoret						
132	Rat (Fischer 344)	2 yr 5 d/wk 6 hr/d		1500			Quast et al. 1988
133	Mouse (B6C3F1)	2 yr 5 d/wk 6 hr/d		1500			Quast et al. 1988

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
	Neurological						
134	Human	6.7 yr avg (occup)		200 F			Maroni et al. 1977
135	Rat (Fischer 344)	2 yr 5 d/wk 6 hr/d		1500			Quast et al. 1988
136	Mouse (B6C3F1)	2 yr 5 d/wk 6 hr/d		1500			Quast et al. 1988
	Reproductive						
137	Rat (Fischer 344)	2 yr 5 d/wk 6 hr/d		1500			Quast et al. 1988
138	Mouse (B6C3F1)	2 yr 5 d/wk 6 hr/d		1500			Quast et al. 1988

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

b Used to derive an acute-duration inhalation minimal risk level (MRL) of 2 ppm; unadjusted exposure concentration divided by an uncertainty factor of 100 (10 for human variability and 10 for use of a LOAEL)

c Used to derive an intermediate-duration inhalation minimal risk level (MRL) of 0.7 ppm; continuous exposure concentration divided by an uncertainty factor of 100 (10 for extrapolation from gerbils to humans and 10 for human variability)

ave = average; Bd wt = body weight; cAMP = cyclic adenosine monophosphate; Cardio = cardiological; cGMP = cyclic guanidine monophosphate; d = day(s); Derm = dermal; DNA = deoxyribonucleic acid; EC50 = effective concentration, 50%; EEG = electroencephalogram; Endo= endocrine; F = female; FEP = flash evoked potential; Gastro = gastrointestinal; Gd = gestation day; GFA = glial fibrillary acid; Gn Pig = guinea pig; Hemato = hematological; hr = hour(s); LC50 = lethal concentration; 50 kill; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); mo = month(s); Musc/skel = musculoskeletal; NS = not specified; NOAEL = no-observed-adverse effect level; occup = occupational; ppm = parts per million; resp = respiratory; SEP somatosensory evoked potential; wk = week(s); x = time(s); yr = year(s)

Figure 3-1. Levels of Significant Exposure to 1,1,1-Trichloroethane- Inhalation

Acute (≤14 days)

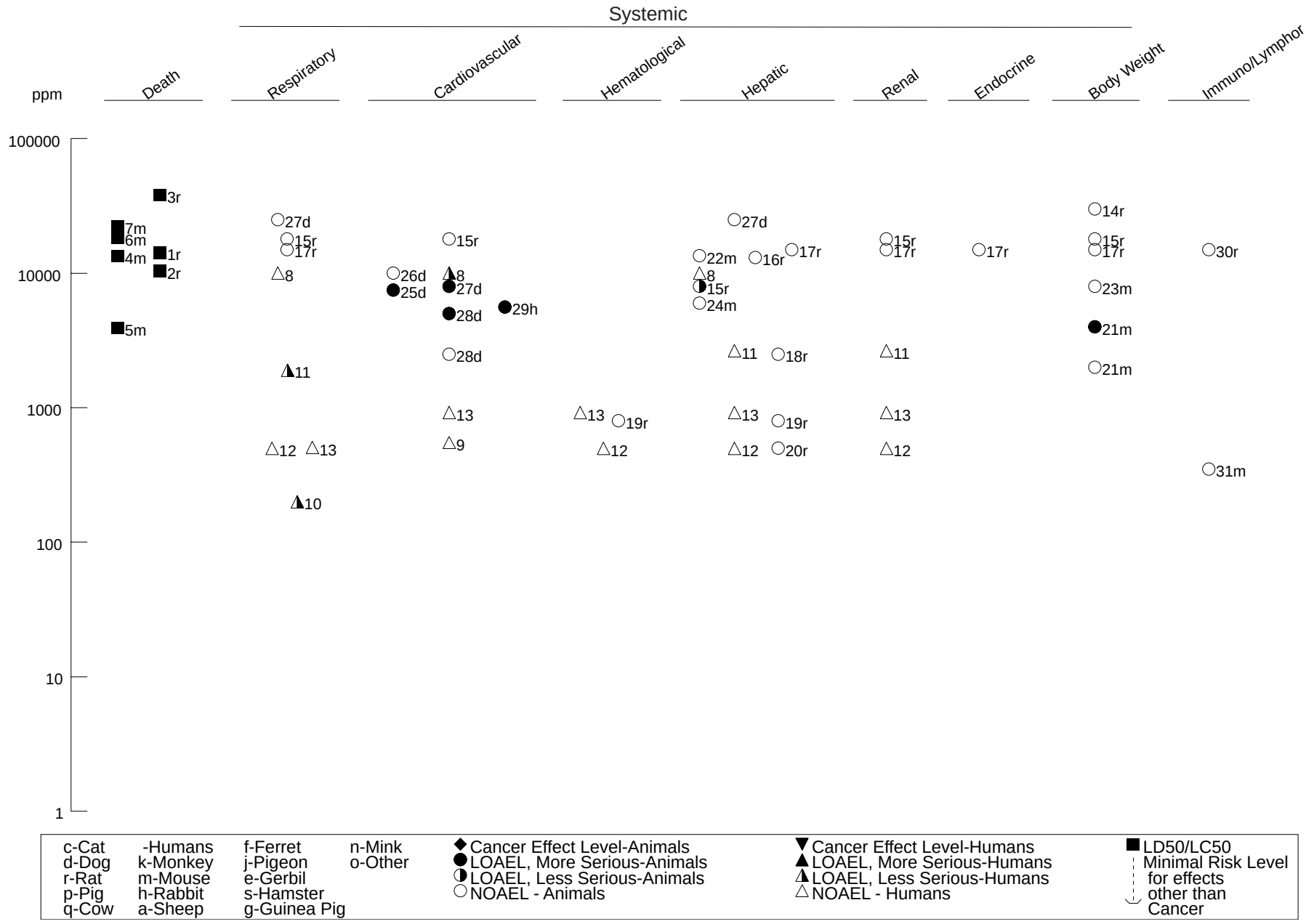


Figure 3-1. Levels of Significant Exposure to 1,1,1-Trichloroethane- Inhalation (*Continued*)

Acute (≤14 days)

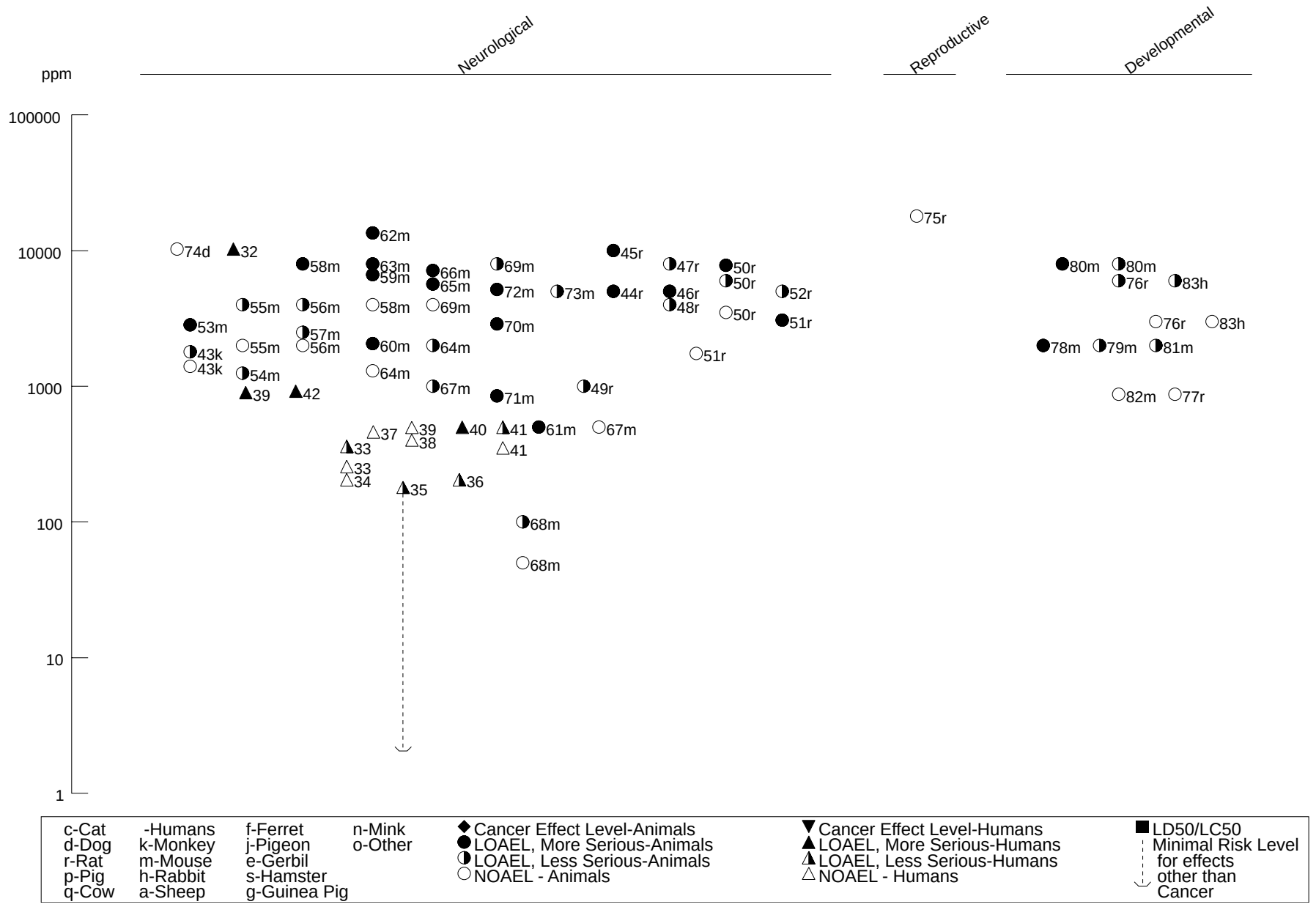


Figure 3-1. Levels of Significant Exposure to 1,1,1-Trichloroethane- Inhalation (*Continued*)

Intermediate (15-364 days)

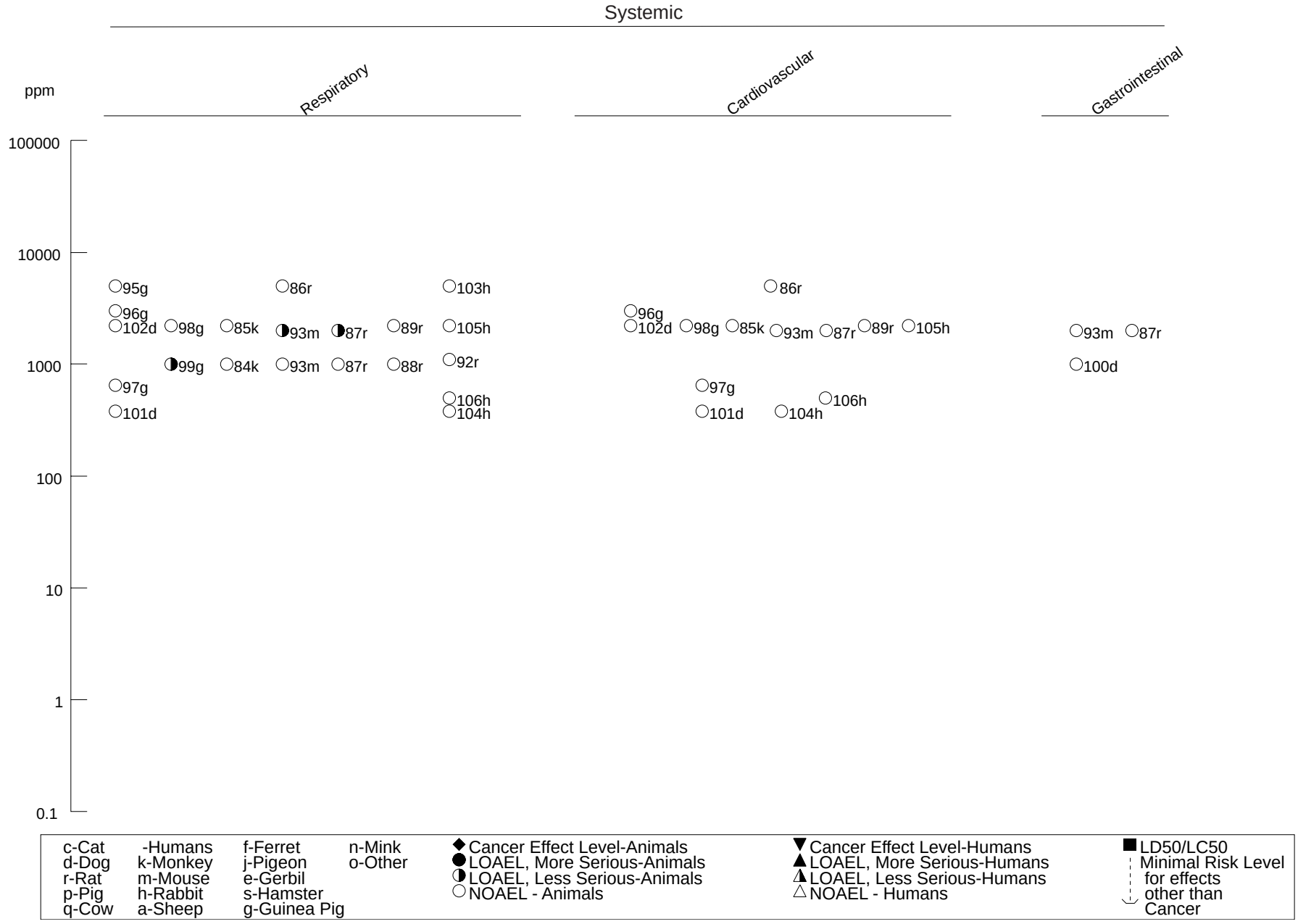


Figure 3-1. Levels of Significant Exposure to 1,1,1-Trichloroethane- Inhalation (*Continued*)

Intermediate (15-364 days)

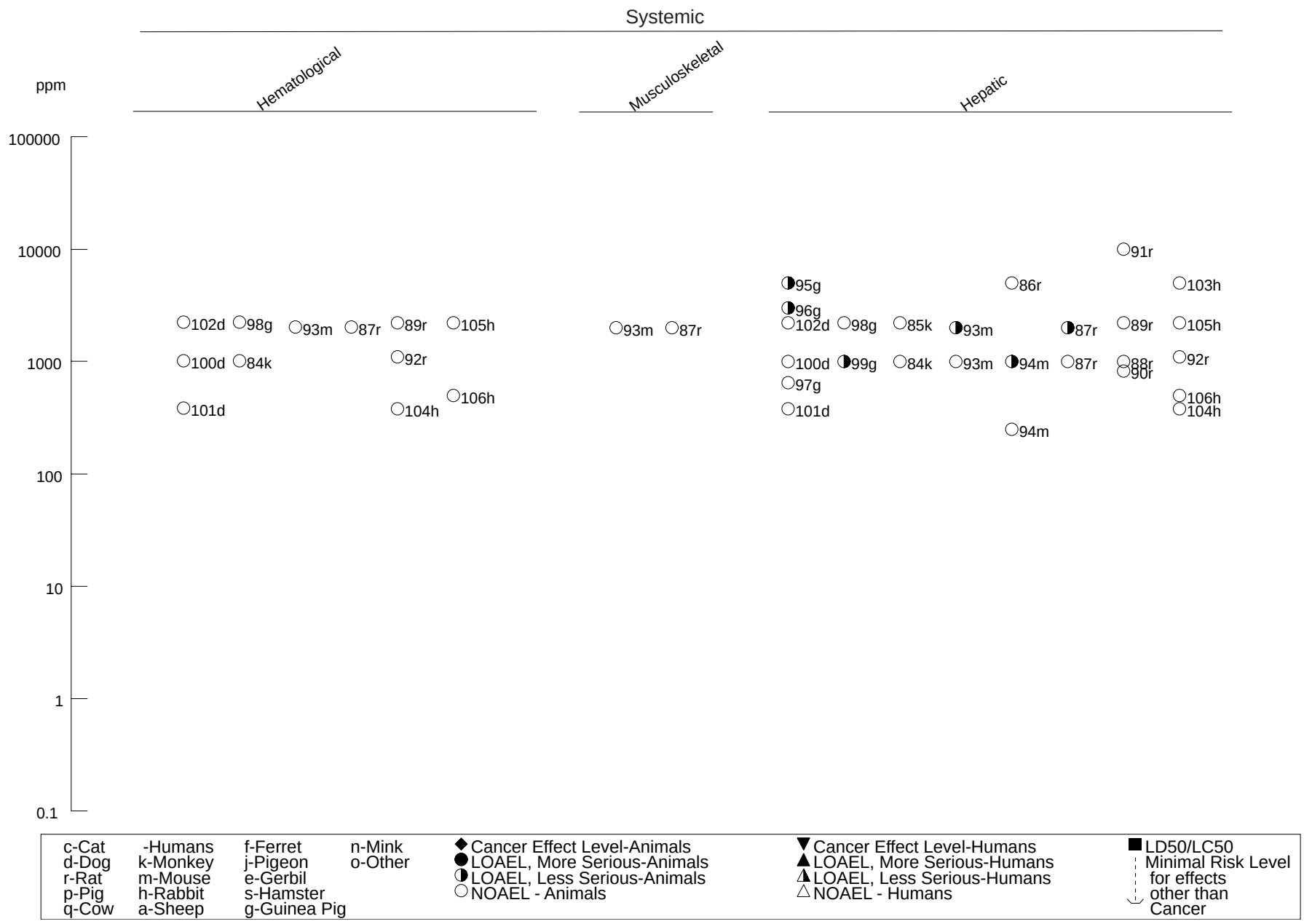


Figure 3-1. Levels of Significant Exposure to 1,1,1-Trichloroethane- Inhalation (*Continued*)

Intermediate (15-364 days)

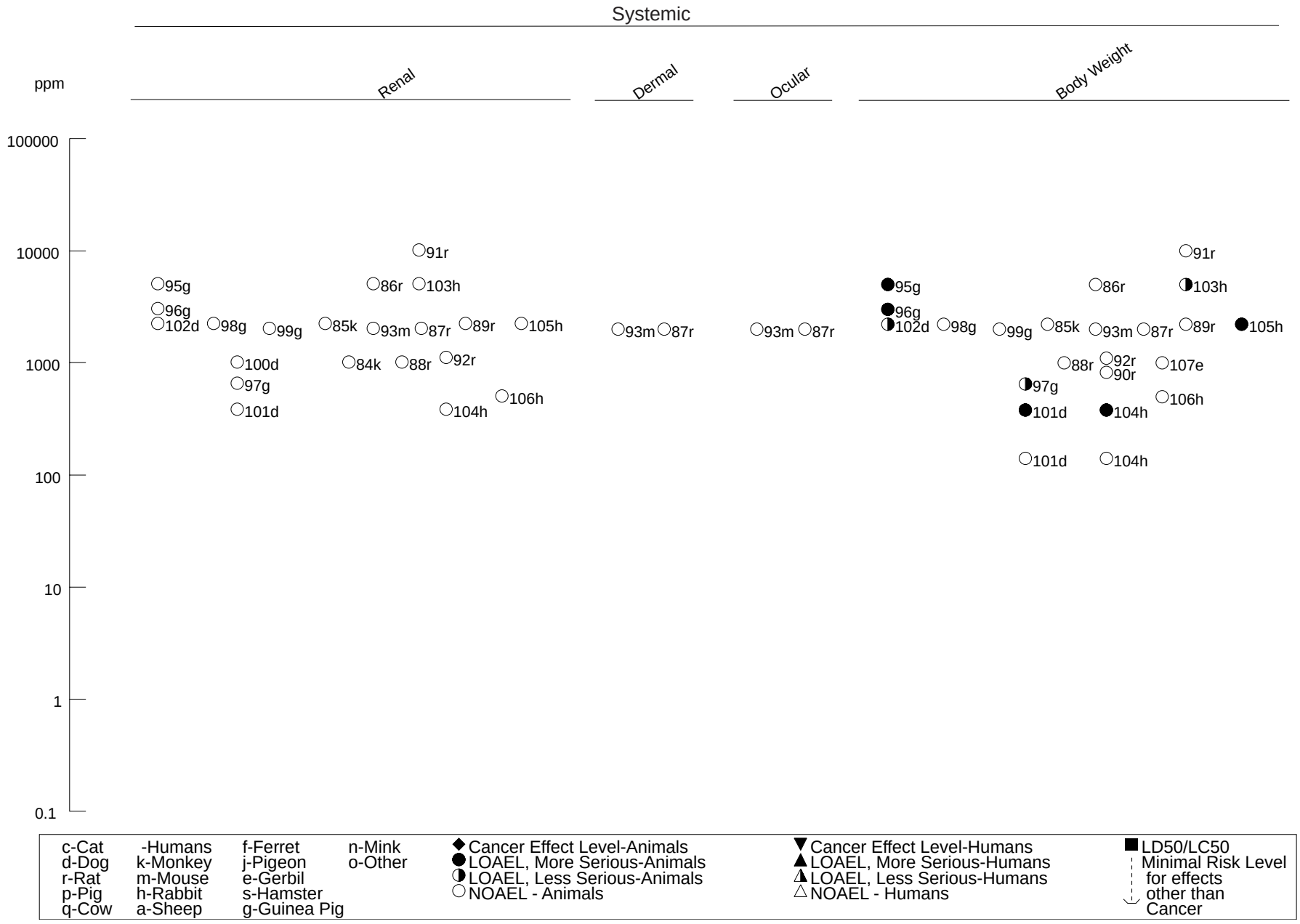


Figure 3-1. Levels of Significant Exposure to 1,1,1-Trichloroethane- Inhalation (*Continued*)

Intermediate (15-364 days)

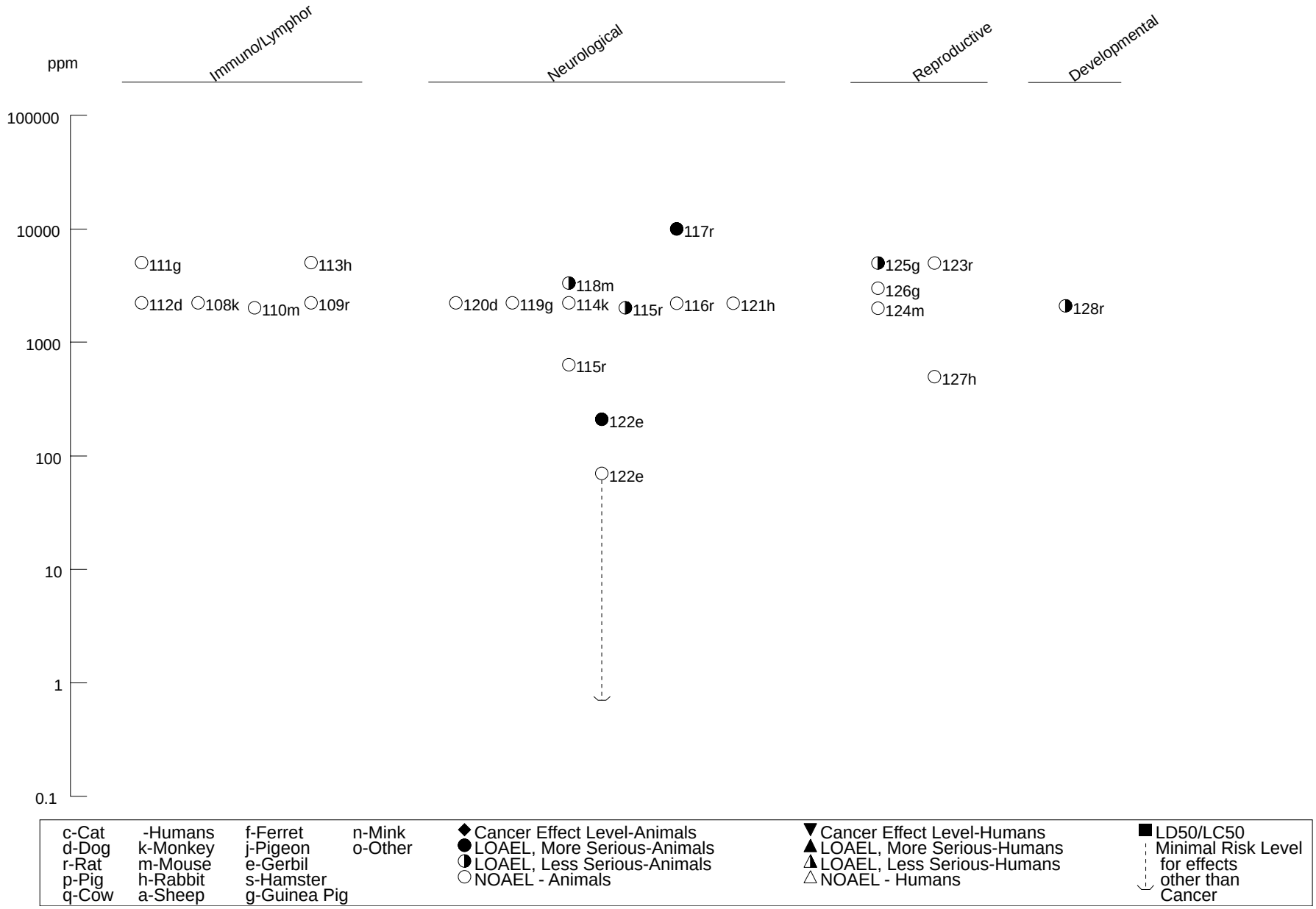


Figure 3-1. Levels of Significant Exposure to 1,1,1-Trichloroethane- Inhalation (*Continued*)

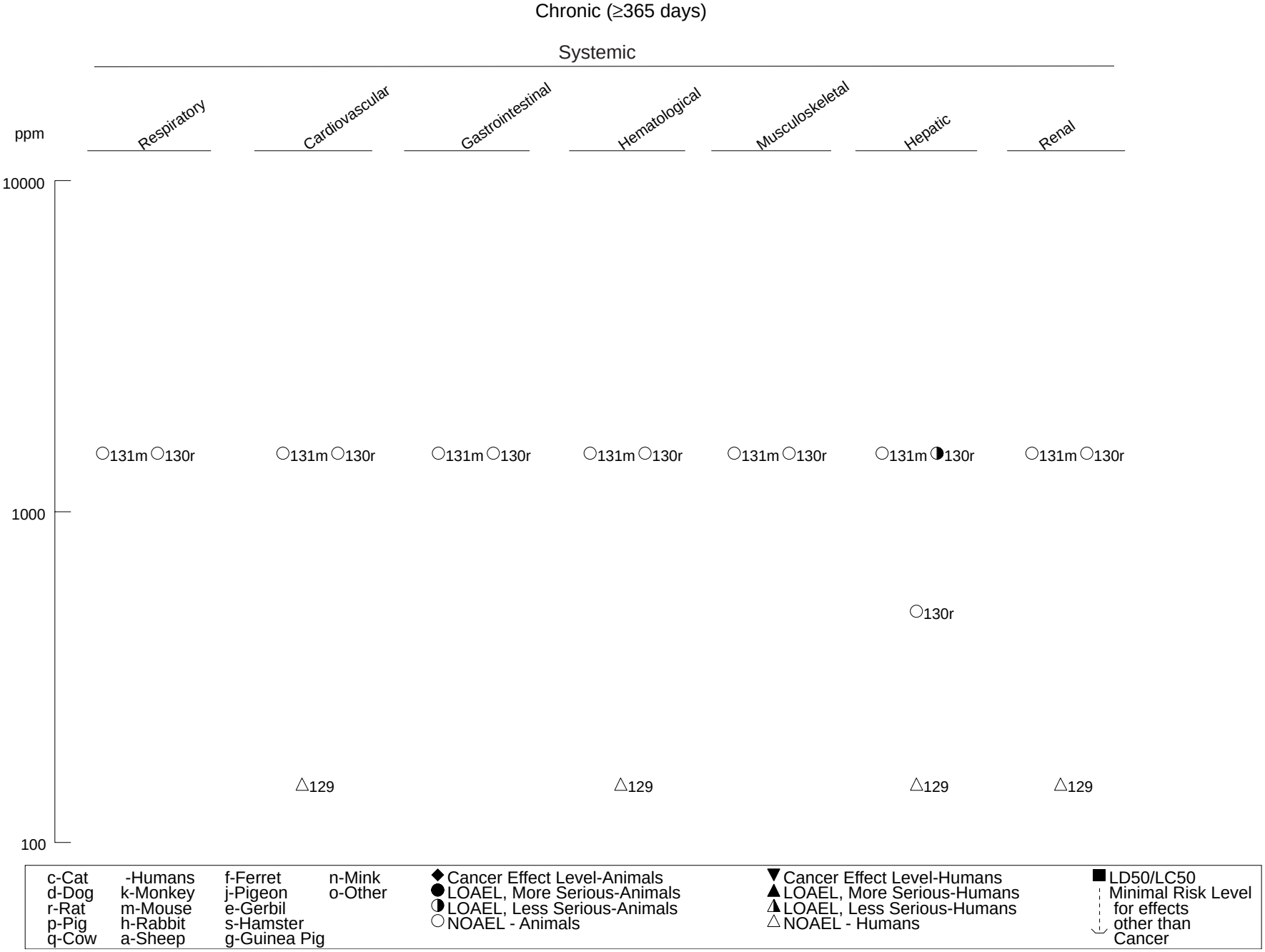
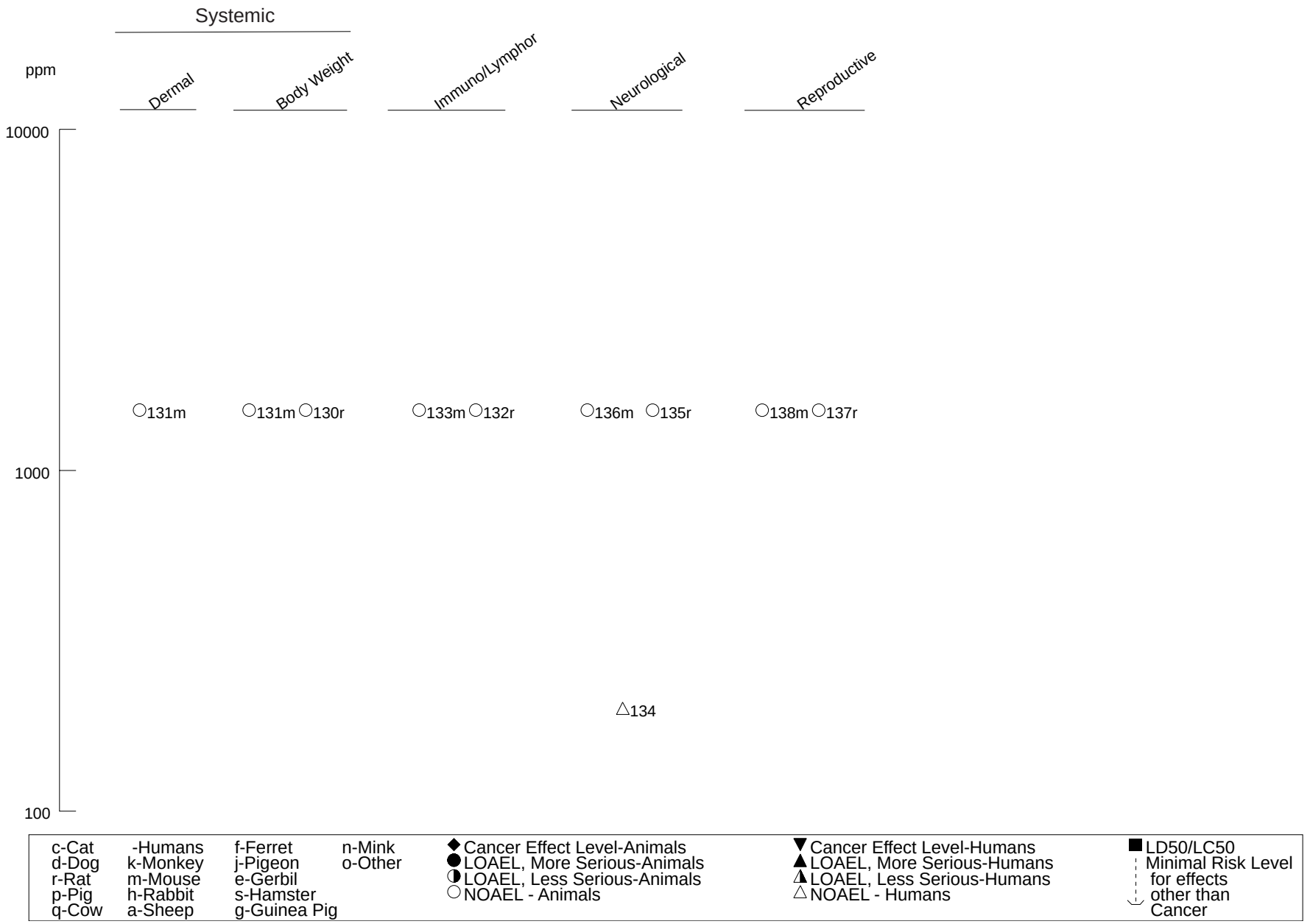


Figure 3-1. Levels of Significant Exposure to 1,1,1-Trichloroethane- Inhalation (*Continued*)

Chronic (≥365 days)



indicate that long-term exposure to low or moderate 1,1,1-trichloroethane concentrations may not influence survival.

3.2.1.2 Systemic Effects

Respiratory Effects. In humans, acute exposure to high concentrations of 1,1,1-trichloroethane can produce respiratory depression (Kelly and Ruffing 1993), leading to death (Hall and Hine 1966; Jones and Winter 1983; Stahl et al. 1969; Winek et al. 1997). Respiratory depression may be a result of generalized central nervous system depression (see the discussion of Neurological Effects in this section). Acute exposure to lower concentrations of 1,1,1-trichloroethane in controlled studies did not affect respiratory rate or volume in humans (Dornette and Jones 1960; Sot et al. 1975; Torkelson et al. 1958). 1,1,1-Trichloroethane may act as a slight respiratory tract irritant, as evidenced by increased concentrations of proinflammatory cytokines in nasal secretions of healthy volunteers exposed to 1,1,1-trichloroethane at a vapor concentration of 200 ppm for 4 hours (Muttray et al. 1999). Chest radiographs from several (unspecified number) of 28 workers exposed to an undetermined concentration of 1,1,1-trichloroethane for about 10 years showed changes consistent with early pneumoconiosis (fibrosis), but this was consistent with known exposure to asbestos and silica (Kelafant et al. 1994).

Death due to respiratory failure has been reported in several species of animals acutely exposed to high 1,1,1-trichloroethane concentrations (Adams et al. 1950; Krantz et al. 1959). Other data on respiratory effects in animals are limited to results of histological examinations of the lungs and related tissues. Tissue lesions were not found in rats or dogs exposed to high concentrations of 1,1,1-trichloroethane for short periods (Adams et al. 1950; Bonnet et al. 1980; Cornish and Adefuin 1966; Herd et al. 1974). Exposure to moderate to high concentrations for intermediate periods (≤6 months) failed to produce pulmonary lesions in most species (Adams et al. 1950; Eben and Kimmerle 1974; MacEwen and Vernot 1974; Prendergast et al. 1967; Torkelson et al. 1958; Truffert et al. 1977), but irritation and inflammation occurred in the lungs of guinea pigs exposed to 1,000 ppm for 3 months (Torkelson et al. 1958). These effects were not found in other studies in which guinea pigs were exposed to lower concentrations or exposed for shorter durations (Adams et al. 1950; Prendergast et al. 1967; Torkelson et al. 1958). Rats and mice exposed to 2,000 ppm 1,1,1-trichloroethane for 3 months developed mild degeneration of the nasal olfactory epithelium (Calhoun et al. 1981). Chronic inhalation of moderate 1,1,1-trichloroethane concentrations did not produce lesions in the respiratory tissues of rats or mice (Quast et al. 1988).

The highest NOAEL values and all reliable LOAEL values for respiratory effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1. Although lung irritation, inflammation, and olfactory epithelium degeneration were found in some species of laboratory animals exposed for intermediate durations in some studies, the weight of evidence suggests that respiratory failure in humans and animals is secondary to central nervous system depression and occurs only after acute exposure to very high concentrations.

Cardiovascular Effects. Inhalation of very high 1,1,1-trichloroethane concentrations for a short period can produce severe cardiac arrhythmias and death in humans. Arrhythmias are thought to be produced indirectly by 1,1,1-trichloroethane by sensitization of the heart to epinephrine (Guberan et al. 1976; MacDougall et al. 1987; Travers 1974). Cardiac sensitization to epinephrine has also been demonstrated in animals exposed to 1,1,1-trichloroethane (Clark and Tinston 1973; Kobayashi et al. 1982). In addition, reduced blood pressure, occasionally severe, has been reported in humans following brief exposure to high concentrations of 1,1,1-trichloroethane (Dornette and Jones 1960; Krantz et al. 1959). Acute exposure to lower concentrations (<1,000 ppm) did not affect clinical cardiovascular parameters such as blood pressure, pulse, heart rate, or electrocardiogram in the humans tested (Gamberale and Hultengren 1973; Torkelson et al. 1958). Myocardial injury, monitored by electrocardiography and echocardiography, was reported in the case of a young male who inhaled typewriter correction fluid (Wodka and Jeong 1991). It should be noted, however, that 1,1,1-trichloroethane may have been only one of several chemicals in the correction fluid.

In humans, long-term exposure to high 1,1,1-trichloroethane vapor concentrations can have toxic effects on the heart that persist beyond the period of exposure. While experiments in animals have shown that arrhythmias produced by 1,1,1-trichloroethane and epinephrine quickly subside after the cessation of exposure (Carlson 1981; Clark and Tinston 1973), three human cases involved ventricular arrhythmias that persisted for 2 weeks or more after solvent exposure ended (McLeod et al. 1987; Wright and Strobl 1984). In all three cases, the subjects had been exposed repeatedly to high (unspecified) 1,1,1-trichloroethane concentrations. Echocardiograms revealed mild left ventricular dilation in one patient and slightly dilated left atrium in another, as well as impaired left ventricle function in both (McLeod et al. 1987). Chronic exposure (<250 ppm) to 1,1,1-trichloroethane had no effect on blood pressure, heart rate, or electrocardiogram in workers surveyed in a matched-pair epidemiology study (Kramer et al. 1978). Similar results were recently reported for a group of 28 workers exposed to unspecified, but high concentrations of 1,1,1-trichloroethane for about 10 years (Kelafant et al. 1994).

Sensitization of the heart to epinephrine-induced arrhythmias has been reported in both rabbits and dogs acutely exposed to high 1,1,1-trichloroethane concentrations (≥5,000 ppm) (Carlson 1981; Clark and Tinston 1973; Reinhardt et al. 1973; Trochimowicz et al. 1974). The effect is rapid, occurring after only a few minutes of exposure, and transitory, quickly disappearing after the end of exposure. In rabbits, there was evidence that susceptibility to arrhythmia increased with exposure duration, and that 1,1,1-trichloroethane itself, not its metabolites, produced the sensitizing effect (Carlson 1981). Among dogs, the effect was similar in normal animals and those with experimentally induced myocardial infarctions; prior damage to the heart did not lower the threshold for cardiac sensitization produced by 1,1,1-trichloroethane (Trochimowicz et al. 1974).

Blood pressure was reduced in dogs acutely exposed to high concentrations of 1,1,1-trichloroethane (>7,500 ppm) (Aoki et al. 1997; Herd et al. 1974; Krantz et al. 1959). This effect was studied in detail by Herd et al. (1974), who reported that the decrease in blood pressure began within 15 seconds of the start of exposure and grew more pronounced as exposure continued. At 8,000–15,000 ppm, the decrease in blood pressure was accompanied by increased myocardial contractility and cardiac output. A decrease in total peripheral resistance was apparently responsible for the decrease in blood pressure at these concentrations. At 20,000–25,000 ppm, blood pressure depression was caused by reductions in myocardial contractility and cardiac output. Blood pressure returned to pre-exposure values within 15 minutes after exposure, but indices of cardiac output and contractility required 45 minutes to recover. The dogs died if the blood pressure dropped too low. Histopathological changes in the heart were not found upon necropsy. In the study of Aoki et al. (1997), the decrease in blood pressure was accompanied by sinus tachycardia and increases in cardiac output, pulmonary vascular resistance, and pulmonary arterial pressure.

The arrhythmogenic and hypotensive properties of 1,1,1-trichloroethane have not been examined in animal studies of longer duration. Cardiovascular end points investigated in longer-term studies include heart weight and histopathology. No cardiovascular lesions were found among several animal species exposed to moderate to high concentrations (≤5,000 ppm) of 1,1,1-trichloroethane for ≤6 months (Adams et al. 1950; Calhoun et al. 1981; Eben and Kimmerle 1974; Prendergast et al. 1967; Torkelson et al. 1958). Chronic inhalation of moderate concentrations (<2,000 ppm) of 1,1,1-trichloroethane did not produce cardiovascular lesions in rats or mice (Quast et al. 1988). The absence of effects detectable by routine histopathology in longer-term studies does not provide convincing evidence for lack of

cardiovascular effects, because even the marked acute effects were not accompanied by changes in histopathology. Overall, however, it appears that cardiotoxicity only occurs at very high exposure levels.

The highest NOAEL values and all reliable LOAEL values for cardiovascular effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1. Cardiovascular effects reported in humans include sensitization of the heart to epinephrine and decreased blood pressure. Both effects were found only after brief exposure to high 1,1,1-trichloroethane concentrations. These effects were also reported in animals, in which they were studied in greater detail. Some evidence from human case reports, although not conclusive, indicates that repeated exposure to high 1,1,1-trichloroethane concentrations may result in cardiovascular effects that persist for some time after the end of exposure. This possibility has not yet been assessed in laboratory animal investigation.

Gastrointestinal Effects. Nausea, vomiting, and diarrhea have been reported in humans exposed to high 1,1,1-trichloroethane concentrations by inhalation (Jones and Winter 1983; McCarthy and Jones 1983; Stewart 1971). Other gastrointestinal end points have not been examined in humans.

Gastrointestinal effects have not been reported in animals exposed to 1,1,1-trichloroethane, although vomiting is not possible in rodents and only histological end points have been studied in animals. Gastrointestinal lesions were not observed among several species of animals exposed to moderate to high concentrations of 1,1,1-trichloroethane for intermediate or chronic durations (Adams et al. 1950; Calhoun et al. 1981; MacEwen and Vernot 1974; Quast et al. 1988; Torkelson et al. 1958).

The highest NOAEL values for gastrointestinal effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1. Acute exposure to high 1,1,1-trichloroethane concentrations may produce nausea and related symptoms in humans, but evidence from animals suggests that long-term exposure will not produce histological changes.

Hematological Effects. No evidence exists that 1,1,1-trichloroethane produces hematological effects in humans. Hematological parameters, including white blood cell count, red blood cell count, hemoglobin, and hematocrit, were unchanged in humans acutely exposed to high or moderate concentrations of 1,1,1-trichloroethane (Sot et al. 1975; Stewart et al. 1961, 1969; Torkelson et al. 1958; Wright and Strobl 1984). Hematological variables were similarly unaffected in workers chronically exposed to low-to-moderate levels of 1,1,1-trichloroethane in a matched-pair epidemiology study

(Kramer et al. 1978). Hemolytic disease was suggested by increases in urinary urobilinogen in several people exposed to high levels of 1,1,1-trichloroethane (Stewart 1971; Stewart et al. 1961), but this possibility was discounted because there was no association between exposure and elevated urinary urobilinogen levels and because other indices of hematological effects were normal.

Hematological effects were not found in animals exposed to 1,1,1-trichloroethane. No exposure-related changes in hematological parameters were found following acute, intermediate, and chronic exposure to moderate to high 1,1,1-trichloroethane concentrations in several species of animals (Calhoun et al. 1981; Eben and Kimmerle 1974; Horiguchi and Horiguchi 1971; Koizumi et al. 1983; Krantz et al. 1959; MacEwen and Vernot 1974; Prendergast et al. 1967; Quast et al. 1988; Torkelson et al. 1958; Truffert et al. 1977).

The highest NOAEL values for hematological effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1. Existing data indicate that 1,1,1-trichloroethane does not produce hematological effects in humans or animals following inhalation exposure.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after inhalation exposure to 1,1,1-trichloroethane.

No musculoskeletal effects were found in animals exposed to 1,1,1-trichloroethane as assessed by histopathological examination. No lesions were found in the muscles or bones of a monkey exposed to a high 1,1,1-trichloroethane concentration for 74 days (Adams et al. 1950), or in rats and mice exposed for intermediate- or chronic-durations to moderate to high concentrations of the chemical (Calhoun et al. 1981; Quast et al. 1988).

The highest NOAEL values for musculoskeletal effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1. Based on existing data, 1,1,1-trichloroethane does not cause musculoskeletal effects in animals after chronic inhalation exposure. The relevance of this information to human health is unknown.

Hepatic Effects. Although there were no indications of liver effects in studies of controlled human exposure to 1,1,1-trichloroethane, data from case reports of overexposed humans suggest that this chemical may produce hepatic effects in humans exposed to high levels.

Serum levels of transaminases and other enzymes, used as indicators of hepatocellular damage (or damage to other tissues or organ systems), were not increased by acute exposure to moderate to high 1,1,1-trichloroethane concentrations in controlled human studies; liver function tests were likewise unaffected (Dornette and Jones 1960; Sot 1975; Stewart et al. 1961, 1969; Torkelson et al. 1958). However, some case studies of individuals exposed to high 1,1,1-trichloroethane concentrations did report elevated serum enzyme levels. Four individuals who had substantial occupational exposure to 1,1,1-trichloroethane had elevated serum glutamic oxaloacetic transaminase (SGOT) levels (Hodgson et al. 1989). An individual studied by Halevy et al. (1980) had elevated levels of serum bilirubin, lactate dehydrogenase (LDH), and alkaline phosphatase, as well as SGOT. It should be noted that SGOT and LDH are present in substantial amounts in myocardial cells as well as hepatocytes, and that elevations in these enzymes could have been the result of myocardial injury. Elevated serum LDH, gamma-glutamyl transpeptidase (GGT), SGOT, and glutamic pyruvic transaminase (SGPT), and pathologic signs of progressive liver disease were noted in a patient who was occupationally exposed to 1,1,1-trichloroethane for several years (Cohen and Frank 1994). Removal of the patient from exposure resulted in improvement of the impaired liver function, although the serum levels of LDH, GGT, SGOT, and SPGT remained higher than normal as long as 14 months following cessation of exposure. Other exposed individuals did not have elevated serum enzyme levels (Stewart 1971; Wright and Strobl 1984). In some cases, histopathological examination revealed mild fatty changes in the liver of individuals exposed to high 1,1,1-trichloroethane concentrations (Caplan et al. 1976; Hall and Hine 1966; Hodgson et al. 1989). In another case, cholestasis was observed (Halevy et al. 1980). Pathological liver effects were observed in two separate case reports of repeated exposure to 1,1,1-trichloroethane in poorly ventilated work areas (Croquet et al. 2003; Texter et al. 1979). Nevertheless, hepatic changes were not observed in most cases.

Chronic exposure to low 1,1,1-trichloroethane levels (<250 ppm) did not affect serum chemistry parameters, including SGOT, SGPT, bilirubin, LDH, GGT, and alkaline phosphatase, in individuals tested as part of a matched-pair epidemiology study (Kramer et al. 1978). Results from tests for hepatic function were unremarkable in 28 workers exposed to unspecified, but high, concentrations of 1,1,1-trichloroethane for approximately 10 years (Kelafant et al. 1994).

1,1,1-Trichloroethane produces mild hepatic effects in animals. The primary effects reported are mild histopathological changes in the liver and effects on liver enzyme activities. Acute exposure to high 1,1,1-trichloroethane concentrations did not affect serum transaminase levels in rats or mice (Carlson

1973; Cornish and Adefuin 1966; Gehring 1968). An increase in transaminase levels would indicate damage to hepatocytes. The rate of deoxyribonucleic acid (DNA) synthesis in the liver also can be used as an indicator of hepatotoxicity. DNA synthesis would be expected to increase in response to cell death. Exposure to 1,100 ppm 1,1,1-trichloroethane produced a 67% increase in DNA synthesis in the livers of exposed rats after 1 week; DNA synthesis returned to control levels throughout the rest of the 15-week study (Truffert et al. 1977). Corresponding histopathological changes were not found throughout the study. Based on these data, measurement of DNA synthesis may be a more sensitive indicator of hepatocellular damage than increases in serum transaminase levels or the presence of readily observable lesions. However, these results have not been verified by additional testing. Only one study actually observed cell death following 1,1,1-trichloroethane exposure; occasional hepatocyte necrosis was seen in mice exposed to 1,000 ppm of 1,1,1-trichloroethane continuously for 14 weeks (McNutt et al. 1975). The first evidence of necrosis was not seen until after 10 weeks of exposure, but within 2 weeks of first occurrence, necrosis could be found in 40% of the exposed mice. In a study of chronic exposure, a slight decrease in the size of hepatocytes in the liver's portal region was seen in high-dose male and female rats at 6, 12, and 18 months, but these effects were not distinguishable from normal geriatric changes at 24 months (Quast et al. 1988).

The most widely reported hepatic effect in studies of 1,1,1-trichloroethane inhalation in animals is fat accumulation in the liver. Such changes are generally reversible and do not necessarily involve impairment of liver function. Histological examination following acute exposure to high concentrations revealed mild, reversible fatty changes in the livers of rats, but not dogs (Adams et al. 1950; Herd et al. 1974). Exposure duration was important in rats; effects were seen in those exposed for 7 hours, but not in those exposed to much higher concentrations for only 2 hours (Adams et al. 1950). In mice, 3-hour exposure to 800 ppm of 1,1,1-trichloroethane appeared to increase liver triglyceride levels, although controls were not included (Takahara 1986a). In studies of intermediate duration, exposure to moderate to high 1,1,1-trichloroethane concentrations produced fatty changes in the livers of rats, mice, and guinea pigs (Adams et al. 1950; Calhoun et al. 1981; McNutt et al. 1975; Torkelson et al. 1958). Fatty changes produced by 1,1,1-trichloroethane in the livers of mice continuously exposed to 1,000 ppm for 14 weeks were described in detail by McNutt et al. (1975). Prominent swelling of centrilobular hepatocytes was visible after the first week of exposure. Swelling was associated with the presence of numerous small vesicles in the cytoplasm. After 4 weeks, the number of microbodies in the cytoplasm was dramatically increased, and lysosomal vesicles were more prominent. Increased liver triglyceride levels were also reported in this study.

Studies of 1,1,1-trichloroethane's effects on liver enzyme activity are inconclusive. Acute inhalation of high concentrations induced the activity of liver microsomal enzymes (e.g., cytochrome P-450, NADPH cytochrome c reductase) in rats and mice (Fuller et al. 1970; Lal and Shah 1970). Continuous exposure to low 1,1,1-trichloroethane levels for 10 days also increased microsomal enzyme activity in rats (Koizumi et al. 1983), but exhibited no effect on liver or red blood cell δ-aminolevulinic acid dehydratase (ALA-D) activity, inhibition of which is an early indicator for disruption of heme synthesis (Koizumi et al. 1984). A 5-day repeated exposure to a moderate concentration decreased microsomal cytochrome P-450 enzyme activity in rats (Savolainen et al. 1977). Intermediate-duration exposure to a moderate concentration had no effect on microsomal enzyme levels in rats (Toftgaard et al. 1981).

The highest NOAEL values and all reliable LOAEL values for hepatic effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1. Mild to moderate hepatic effects were occasionally reported in humans and animals exposed to 1,1,1-trichloroethane. These include indications of fatty liver and, in one case, cholestasis in humans and manifestations of hepatic necrosis and fatty changes in animals. These changes were not found in many studies, and results were mixed in many studies that did show effects. Evidence of hepatocellular damage and necrosis, changes in liver enzyme activity, and fat accumulation generally were reported following exposure to high concentrations in acute- and intermediate-duration studies in animals. The severity of the effects appears to be related to exposure dose and duration. It is unclear whether 1,1,1-trichloroethane may induce or inhibit microsomal enzyme activity in rats. In any case, the implications of effects on liver enzyme activity for toxicity are not clear, mainly because of the contradictory nature of the reported results.

Renal Effects. A few studies in humans have examined 1,1,1-trichloroethane's effects on select parameters of serum and urine chemistry that are related to renal function. Evidence of renal impairment was found in only one case report (Halevy et al. 1980). The individual in this case, who was exposed for 4 hours in a small room without ventilation (probably to high levels) presented with proteinuria, elevated blood creatinine, and reduced creatinine clearance, all of which were maximal at time of admission and returned to normal within 10 days. In addition to having prominent renal effects, this individual was unusual in having prominent liver effects and only minimal neurological effects. The authors suggested that an individual hypersensitivity might explain the atypical course of 1,1,1-trichloroethane intoxication. No effects were found on subsequent evaluations. No evidence of nephrotoxicity was found in other studies, although the end points examined, such as blood urea nitrogen (BUN), are only adequate for

detecting serious decrements in function. An increase in the BUN level would indicate decreased elimination of nitrogenous waste by the kidneys (impairment of kidney function). Acute exposure to 1,1,1-trichloroethane had no effect on BUN or uric acid levels in humans exposed to high or moderate concentrations (Sot et al. 1975; Stewart 1971; Stewart et al. 1969; Wright and Strobl 1984). Chronic-duration exposure of workers to <250 ppm of 1,1,1-trichloroethane had no effect on BUN, uric acid, or other serum indicators of nephrotoxicity in a matched-pair epidemiology study (Kramer et al. 1978).

Acute-duration exposure to high 1,1,1-trichloroethane concentrations failed to produce kidney lesions in rats (Adams et al. 1950; Bonnet et al. 1980; Cornish and Adefuin 1966; Krantz et al. 1959), although relative kidney weight was increased slightly at 12,000 ppm in the one study in which it was measured (Adams et al. 1950). Exposure of several animal species to moderate to high concentrations for intermediate durations had no apparent effect on kidney weight or histopathology, or relevant serum chemistry parameters (Adams et al. 1950; Calhoun et al. 1981; Eben and Kimmerle 1974; Kjellstrand et al. 1985b; MacEwen and Vernot 1974; Prendergast et al. 1967; Torkelson et al. 1958; Truffert et al. 1977). Chronic inhalation of 1,1,1-trichloroethane did not affect the kidneys of rats or mice (Quast et al. 1988).

The kidney does not appear to be a target organ for 1,1,1-trichloroethane toxicity. The highest NOAEL values and all reliable LOAEL values for renal effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

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

Information in animals is limited. In an acute-duration study, no histopathological changes were seen in the adrenals of rats after a single 2-hour exposure to up to 15,000 ppm 1,1,1-trichloroethane (Cornish and Adefuin 1966). Plasma corticosterone levels were significantly decreased in rats after inhalation exposure to 1,1,1-trichloroethane at a concentration of 3,500 ppm for 30 minutes or 5,000 ppm for 10 or 30 minutes; the highest exposure level also resulted in significantly reduced plasma adrenocorticotropic hormone (Pise et al. 1998). The NOAEL and LOAEL values for endocrine effects from these studies are recorded in Table 3-1 and plotted in Figure 3-1.

Dermal Effects. Available information in humans is limited to a case-control report in which significantly increased risk of systemic sclerosis (scleroderma) was associated with purported exposure to 1,1,1-trichloroethane in some Michigan women (Dow Corning Corp. 1994). However, a larger follow-up case-control study conducted on 660 women diagnosed with scleroderma between 1980 and 1992 in Michigan and Ohio found no significant association between exposure to 1,1,1-tricloroethane and scleroderma (Garabrant et al. 2003). In neither case control study could 1,1,1-trichloroethane exposure be quantified.

Mice exposed continuously to 4,000 ppm 1,1,1-trichloroethane for 4 days exhibited dull fur coats (Evans and Balster 1993); this effect, however, was the result of direct contact with the chemical in the air (see Section 3.2.3.2). Intermittent exposure of rats or mice to 2,000 ppm 1,1,1-trichloroethane for 90 days (Calhoun et al. 1981) or to 1,500 ppm for 2 years (Quast et al. 1988) had no effect on the incidence of dermal lesions. NOAEL and LOAEL values derived from these studies are recorded in Table 3-1 and plotted in Figure 3-1.

Ocular Effects. When 1,1,1-trichloroethane vapor concentrations exceeded 1,000 ppm, volunteers exposed for 20–73 minutes reported mild eye irritation (Stewart et al. 1961). Eye irritation was not indicated in other volunteers exposed for 186 minutes at a vapor concentration of approximately 500 ppm.

Mice exposed continuously to 4,000 ppm 1,1,1-trichloroethane for 4 days exhibited eye irritation during exposure (Evans and Balster 1993). All of the above effects, however, were probably due to direct contact of the chemical in the air with the eye (see Section 3.2.3.2). Intermittent exposure of rats or mice to 2,000 ppm 1,1,1-trichloroethane for 90 days (Calhoun et al. 1981) or to 1,500 ppm for 2 years (Quast et al. 1988) had no effect on the incidence of ocular lesions. NOAEL and LOAEL values derived from these studies are recorded in Table 3-1 and plotted in Figure 3-1.

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

Acute inhalation exposure to high concentrations of 1,1,1-trichloroethane did not affect body weight in rats (Adams et al. 1950; Bonnet et al. 1980; Cornish and Adefuin 1966). However, mice exposed continuously to 4,000 ppm 1,1,1-trichloroethane for 4 days experienced a 26% reduction in body weight throughout the exposure period (Evans and Balster 1993). In studies of intermediate duration, significant

reductions in body weight gain were reported in guinea pigs exposed to 650 ppm (Adams et al. 1950) and rabbits and dogs exposed continuously to 377 ppm (Prendergast et al. 1967). Other intermediate-duration studies of various species (including those mentioned above) found no compound-related effects on body growth, even at high concentrations (Adams et al. 1950; Calhoun et al. 1981; Eben and Kimmerle 1974; Kjellstrand et al. 1985b; Kyrklund et al. 1988; MacEwen and Vernot 1974; Prendergast et al. 1967; Rosengren et al. 1985; Toftgaard et al. 1981; Torkelson et al. 1958; Truffert et al. 1977). Body weight gain was reduced in a concentration-dependent manner in female rats chronically exposed to 1,1,1-trichloroethane (Quast et al. 1988). Body growth was not affected in male rats or male or female mice chronically exposed to the same concentrations. Food consumption was not monitored in the available studies.

Changes in body weight can be produced in a number of ways (e.g., effects on palatability of food, absorption of nutrients, energy metabolism). In the case of 1,1,1-trichloroethane, it is possible that recurring central nervous system depression produced by repeated exposure may be responsible for the reduced body weight gain, by suppression of appetite and food intake. Due to the large number of factors that might affect body weight, assessing the potential relationship between isolated occurrences of reduced body weight gain in animals and possible effects of 1,1,1-trichloroethane on growth of humans is difficult. In any case, no body weight effects from levels found near NPL hazardous waste sites would be expected.

The highest NOAEL values and all reliable LOAEL values for body weight effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.3 Immunological and Lymphoreticular Effects

No information was located regarding immunological effects in humans after inhalation exposure to 1,1,1-trichloroethane. However, lymphoreticular effects, specifically spleen congestion, have been observed at autopsy in cases of acute accidental exposure to high concentrations of 1,1,1-trichloroethane (Gresham and Treip 1983; Stahl et al. 1969).

The effect of acute inhalation of 1,1,1-trichloroethane vapor on immune response in mice was studied by Aranyi et al. (1986). Mice received a single 3-hour exposure to 359 ppm of 1,1,1-trichloroethane. Susceptibility to respiratory infection was tested by challenge with *Streptococcus zooepidemicus* during

exposure. Mortality was similar in test and control mice, indicating no effect on susceptibility to bacteria. To test the effect of inhalation exposure to 1,1,1-trichloroethane on the bactericidal activity of alveolar macrophages, mice were exposed to radiolabeled 35S-*Klebsiella pneumoniae,* and the percentage of bacteria killed was recorded. No difference was found between test and control mice. The same results were found in both tests when mice were exposed under similar conditions for 5 days.

No histopathological alterations were observed in the spleen of rats exposed for 2 hours to up to 15,000 ppm 1,1,1-trichloroethane (Cornish and Adefuin 1966). Longer-term studies of immunological effects in animals exposed to 1,1,1-trichloroethane by inhalation were limited to gross and microscopic examination of the spleen, thymus, and lymph nodes. No effect on spleen weight or histopathology was reported among several species exposed to moderate to high 1,1,1-trichloroethane concentrations in studies of intermediate duration (Adams et al. 1950; Calhoun et al. 1981; Kjellstrand et al. 1985b; Prendergast et al. 1967; Torkelson et al. 1958). No exposure-related effects were found upon histopathological examination of the spleen and thymus after chronic exposure to ≤1,750 ppm in rats and 1,500 ppm in mice (Quast et al. 1978, 1988).

The highest NOAEL values for immunological effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1. The existing data suggest that 1,1,1-trichloroethane may not produce toxic effects on the immune system, but sensitive immunological end points have not been examined in humans or animals.

3.2.1.4 Neurological Effects

1,1,1-Trichloroethane produces central nervous system depression, increasing with exposure concentration from mild motor impairment to euphoria, unconsciousness, and death in humans. Low concentrations reportedly produce impaired performance in tests designed to measure variables such as manual dexterity, eye-hand coordination, perceptual speed, and reaction time (Gamberale and Hultengren 1973; Mackay et al. 1987). Results using subjective assessment techniques indicate that behavioral changes may not be apparent to those exposed. Syntactic reasoning remained intact, and distractibility actually improved in the study by Mackay et al. (1987), suggesting that impairment produced by 1,1,1-trichloroethane may be task-specific. In other studies, comparable exposure conditions did not produce significant psychomotor effects (Salvini et al. 1971) or produced only weak effects (Savolainen et al. 1981). Although these studies examined some of the same parameters, such as reaction time, different

analytical methods were used and different subpopulations were tested. Laine et al. (1996) found no subjective symptoms and no significant effects on EEG, visual evoked potentials, or equilibrium among healthy male volunteers exposed to a time-weighted average concentration of 200 ppm of 1,1,1-trichloroethane for 5 hours, including six 10-minute periods of exercise. In another study, a 4-hour inhalation exposure of healthy male volunteers to 200 ppm of 1,1,1-trichloroethane resulted in significantly increased subjective tiredness scores and EEG changes consistent with increased drowsiness (Muttray et al. 2000). Based on the LOAEL of 175 ppm for reduced performance in psychomotor tests identified by Mackay et al. (1987), an acute inhalation MRL of 2 ppm was calculated as described in the footnote in Table 3-1.

Gross neurobehavioral effects, such as disturbances of equilibrium and coordination, occur in humans following acute exposure to 1,1,1-trichloroethane concentrations between 1,000 and 2,000 ppm (Sot et al. 1975; Stewart et al. 1961, 1969; Torkelson et al. 1958). These effects are more obvious at higher exposure concentrations (Torkelson et al. 1958). An increase was noted in the amplitude of alpha activity in electroencephalograms from individuals acutely exposed to moderate concentrations of 1,1,1-trichloroethane (Sot et al. 1975). The significance of this effect is unknown, especially since it persisted for several days, but it occurred at an exposure level that produced no effect on equilibrium or coordination. Visual evoked response was not affected in this study. Complaints of lightheadedness were also reported at moderate levels (Stewart et al. 1961). High 1,1,1-trichloroethane concentrations are inhaled intentionally by some people to experience these and related effects of intoxication.

Inhalation of high 1,1,1-trichloroethane concentrations can produce anesthesia in humans (Dornette and Jones 1960). Dornette and Jones (1960) tested the use of 1,1,1-trichloroethane as a general anesthetic in 50 hospital patients. The effective concentration for induction of anesthesia varied from 10,000 to 26,000 ppm. Onset of anesthesia was extremely rapid, taking place within 2 minutes of the start of exposure. Maintenance of light anesthesia for 2 hours required 6,000–22,500 ppm. Recovery from anesthesia occurred within 5 minutes of the end of exposure. In this study, 1,1,1-trichloroethane was co-administered with nitrous oxide and oxygen, and the effect of 1,1,1-trichloroethane without nitrous oxide was not measured.

Central nervous system depression can cause respiratory failure, the most prevalent cause of death in humans exposed to high 1,1,1-trichloroethane vapor concentrations (Hall and Hine 1966; Jones and Winter 1983; Stahl et al. 1969). Death from inhalation of 1,1,1-trichloroethane is often preceded by

unconsciousness (Gresham and Treip 1983; Travers 1974). Half of the cases of industrial overexposure to 1,1,1-trichloroethane in Great Britain between 1961 and 1980 resulted in unconsciousness; most that did not indicate unconsciousness reported other central nervous system symptoms (McCarthy and Jones 1983). In one industrial accident (Silverstein 1983), two affected men, as well as several of their rescuers, fell unconscious. Persistent coma, with no evidence of improvement 6 months later, was reported for a 17-year-old male who had attempted suicide by inhaling 1,1,1-trichloroethane in typewriter correction fluid (del Amo et al. 1996).

Two studies of long-term occupational exposures found no exposure-related neurological effects. In the first study, the highest exposure ranged from 200 to 990 ppm (Maroni et al. 1977). No exposure-related effects were found, based on the results of subjective questionnaires, neurological examinations, and psychological tests. The authors reported that definite conclusions as to 1,1,1-trichloroethane's neurotoxicity in humans could not be drawn due to the small study population (seven or eight subjects per group) and what the authors felt was a relatively short exposure duration (6.7-year average). In the second study, workers exposed to 1–46 ppm of 1,1,1-trichloroethane were also exposed to low concentrations of toluene (1–4 ppm) and xylene (0–7 ppm) (Cherry et al. 1983). No differences were found between exposed and unexposed workers in tests of reaction time and cognition. Subjective responses indicated greater deterioration of mood in exposed workers, but this may not have been related to exposure. The 1,1,1-trichloroethane concentrations to which workers were exposed in this study were lower than those producing effects in experimental studies. A recent study of 28 subjects occupationally exposed to high (near anesthetic levels) unspecified concentrations of 1,1,1-trichloroethane over a period of 10 years revealed deficits in memory and in several components of balance (Kelafant et al. 1994); it was the investigators' opinion that the overall evidence was suggestive of toxic exposure. Deficits in memory, attention, and concentration were diagnosed in a 45-year-old male who had been heavily exposed to 1,1,1-trichloroethane, as well as dichloromethane, for 15 years (Garnier et al. 1991). Although the patient’s brain function slowly improved following removal from exposure, lingering memory deficit was noted 5 years later.

The principal neurological effects observed in animals exposed to 1,1,1-trichloroethane are signs of central nervous system depression, such as impaired performance in behavioral tests, ataxia, and unconsciousness, and are similar to those seen in humans. Relatively subtle behavioral effects in several species of animals have been reported following acute-duration exposure to 1,1,1-trichloroethane concentrations in the 700–14,000 ppm range (Halogenated Solvents Industry Alliance 1991; Balster et al.

1982, 1997; Bowen and Balster 1996, 1998; Bowen et al. 1996a, 1996b; DeCeaurriz et al. 1983; Geller et al. 1982; Horiguchi and Horiguchi 1971; Kjellstrand et al. 1985a, 1990; Moser and Balster 1985, 1986; Moser et al. 1985; Mullin and Krivanek 1982; Páez-Martínez et al. 2003; Warren et al. 1997, 1998, 2000; Wiley et al. 2002; Woolverton and Balster 1981; You et al. 1994). These behavioral changes were readily reversible and generally involved effects on neuromuscular tests or learned behaviors. Studies using operant conditioning reflect effects of 1,1,1-trichloroethane in animals that are comparable to psychological changes in humans. Behavioral changes are generally considered to indicate neurological effects.

Neurophysiological changes have also been reported during acute-duration inhalation exposure to 1,1,1-trichloroethane (Halogenated Solvents Industry Alliance 1991). Exposure of rats to 2,000 ppm produced readily apparent changes in flash-evoked potential (FEP) and electroencephalogram (EEG), and more subtle changes in the somatosensory-evoked potential (SEP) when the rats were tested during exposure. Exposure to 1,000 ppm produced similar, but less marked, changes in the same measures. Continuous exposure of mice to moderate (500 ppm) concentrations of 1,1,1-trichloroethane for 4 days resulted in a withdrawal syndrome characterized by handling-induced seizures and reduced threshold to pentylenetetrazol-induced seizures after exposure ceased (Evans and Balster 1993). This effect could be prevented by central nervous system depressants, but not by anticonvulsants.

Acute-duration exposure to high 1,1,1-trichloroethane concentrations produced intoxication and incoordination in rats and mice (Adams et al. 1950; Bowen et al. 1996a, 1996b; Clark and Tinston 1982; Hougaard et al. 1984; Lazarew 1929), and elevation of the threshold for pentetrazole-induced seizures in mice (DeCeaurriz et al. 1981). Exposure to 23,000 ppm produced ataxia, followed by unconsciousness and death due to respiratory failure in mice (Woolverton and Balster 1981). A progression from ataxia to lethargy, loss of motor function, and prostration produced by 1,1,1-trichloroethane has been observed in a variety of species, including rats, mice, dogs, and monkeys (Adams et al. 1950; Bonnet et al. 1980; Dow Chemical Co. 1988; Gehring 1968; Krantz et al. 1959; Lazarew 1929; Torkelson et al. 1958).

A comprehensive 13-week neurotoxicity study in rats included grip strength measures, a battery of observational measures, an electrophysiological test battery, and a neuropathology examination (Mattsson et al. 1993). The only notable finding was a significant deficit in forelimb grip performance in both male and female rats exposed to high levels (2,000 ppm) that persisted at least 7 weeks beyond the end of the exposure period. Histopathological and electrophysiological studies found no evidence of neuropathy in

the forelimb that might account for this result. The authors hypothesized that sedative properties of 1,1,1-trichloroethane may have been responsible by allowing the animals to become more relaxed and, consequently, more habituated to the test procedure. No effects were found at moderate levels (630 ppm). The lack of neurophysiological effects at concentrations that produced such effects in the acute-duration study by Halogenated Solvents Industry Alliance (1991) reflects the fact that testing was performed during exposure in the acute-duration study and 65 hours after the end of exposure in the intermediate-duration study.

Histopathological changes in the brain and spinal cord are not characteristic of 1,1,1-trichloroethane exposure and have not been reported when these structures have been examined (Herd et al. 1974; Krantz et al. 1959; Mattsson et al. 1993; Prendergast et al. 1967; Quast et al. 1978, 1988); however, researchers who have subjected gerbils to continuous, intermediate-duration exposure to 1,1,1-trichloroethane have reported changes in the brain that indicate physical damage. Four months after exposure had been discontinued, there was a significant increase in the level of glial fibrillary acid (GFA) protein in the sensorimotor cerebral cortex following exposure to 210 ppm of 1,1,1-trichloroethane (Rosengren et al. 1985). Since this protein is the main protein subunit of astroglial filaments and is found mainly in fibrillary astrocytes, an increase in its occurrence indicates the formation of astroglial fibrils, which are formed in response to brain injury. Therefore, increased GFA protein is associated with astrogliosis and central nervous system damage. These changes produced by 1,1,1-trichloroethane in this study were irreversible, or at least persistent. An intermediate-duration inhalation MRL of 0.7 ppm was derived for 1,1,1-trichloroethane based on the results of this study, as described in the footnote in Table 3-1. A second study, in which gerbils were exposed to 70 ppm of 1,1,1-trichloroethane by the same protocol, was conducted by Karlsson et al. (1987). DNA content was used to measure cell density in different parts of the brain following exposure. Significantly decreased DNA content was found in the posterior cerebellar hemisphere, anterior cerebellar vermis, and hippocampus. These results could be caused by decreased cell density, possibly because of cell loss either by cell death or inhibition of nonneuronal cell acquisition in these areas, but the significance of these changes is uncertain. These methods of ascertaining physical damage to the brain have not been applied to other species.

1,1,1-Trichloroethane also produced changes in brain metabolism in rats and mice. Folbergrova et al. (1984) found a number of changes in cerebral cortical metabolism in rats exposed to high levels. Decreased glucose consumption and blood flow have also been documented in rats (Hougaard et al. 1984). Exposure of rats and mice to low-to-moderate 1,1,1-trichloroethane concentrations resulted in

altered brain levels of cyclic nucleotides (Nilsson et al. 1986a, 1986b; You and Dallas 2000). The importance of the effects on cyclic nucleotides may lie in their altered capacity to act as secondary messengers within the cells, although the toxicological significance of this effect is unknown. No effect on the levels of protein, glutathione, acid proteinase, or ribonucleic acid (RNA) in the brain was found in rats acutely exposed to low concentrations of 1,1,1-trichloroethane (Savolainen et al. 1977). Continuous exposure to 1,200 ppm, but not lower doses, of 1,1,1-trichloroethane for 30 days altered the fatty acid composition of ethanolamine phosphoglyceride isolated from the cerebral cortex in rats (Kyrklund and Haglid 1991; Kyrklund et al. 1988).

1,1,1-Trichloroethane may share discriminate-stimulus properties with both pentobarbital and ethanol (Rees et al. 1987a, 1987b). Rees et al. (1987a) trained mice to press one lever in response to pentobarbital injection and another in response to saline injection. In this way, mice could "tell" the investigator when they were injected with pentobarbital. Upon inhalation of 1,1,1-trichloroethane for 20 minutes, there was a concentration-dependent increase in the percentage of time mice pressed the pentobarbital lever, indicating that the mice were generalizing the effects of pentobarbital to those of 1,1,1-trichloroethane. The results were similar in the second study (Rees et al. 1987b), in which the mice were trained to discriminate between ethanol and saline, and then exposed to 1,1,1-trichloroethane. These studies suggest that mice did not discriminate between the neurological effects of moderate to high concentrations of 1,1,1-trichloroethane and those of pentobarbital and ethanol.

The highest NOAEL values and all reliable LOAEL values for neurological effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1. The acute depressive effect of 1,1,1-trichloroethane in both humans and animals progresses from subtle behavioral effects at low-to-moderate concentrations to unconsciousness at high concentrations. There is evidence to suggest that 1,1,1-trichloroethane does not produce permanent neurological effects in humans. A study in gerbils, however, has produced evidence of lasting physical damage to the nervous system (astrogliosis) following prolonged continuous exposure to low concentrations (210 ppm) of this chemical. More data are needed to determine whether these results/observations are relevant for determining human risk.

3.2.1.5 Reproductive Effects

Limited information is available regarding the reproductive toxicity of 1,1,1-trichloroethane in humans, and exposure levels have not been quantified. Taskinen et al. (1989) conducted a case-control

epidemiology study to investigate the relationship between adverse pregnancy outcomes (spontaneous abortions and congenital malformations) and occupational exposure of fathers to organic solvents, including 1,1,1-trichloroethane, during spermatogenesis for the 80 days prior to conception. No relationship was found between exposure to 1,1,1-trichloroethane and adverse pregnancy outcomes. An apparent decrease in fertility (as measured by number of menstrual cycles required for wife to become pregnant) was noted in Finnish male workers with exposure to 1,1,1-trichloroethane, but the difference from controls was not statistically significant (Sallmén et al. 1998).

Studies in several animal species found no evidence that 1,1,1-trichloroethane has adverse reproductive effects. Histological examination of male and female reproductive tissues following acute-, intermediate-, and chronic-duration exposure to 1,1,1-trichloroethane revealed no exposure-related changes in rats, mice, or rabbits (Adams et al. 1950; Calhoun et al. 1981; Eben and Kimmerle 1974; Quast et al. 1988; Torkelson et al. 1958; Truffert et al. 1977); however, varying degrees of testicular degeneration were observed in male guinea pigs exposed to 5,000 ppm 1,1,1-trichloroethane for 45 days (Adams et al. 1950). One intermediate-duration study used blood chemistry analyses to determine reproductive effects. Continuous exposure to moderate levels of 1,1,1-trichloroethane vapor had no effect on butyrylcholinesterase activity in mice, which suggests that exposure did not have any effect on testosterone activity (Kjellstrand et al. 1985b). Testosterone appears to play a major role in regulating butyrylcholinesterase activity, and, although activity of this enzyme may change in the absence of an effect on testosterone, it is unlikely that an effect on testosterone levels would not be reflected by a change in butyrylcholinesterase activity.

The highest NOAEL values for reproductive effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1. Based on the existing data, the reproductive system does not appear to be a target of 1,1,1-trichloroethane toxicity following inhalation exposure; however, the reproductive toxicity of this chemical cannot be evaluated fully due to the limited human data available and the lack of inhalation studies of reproductive function in animals.

3.2.1.6 Developmental Effects

Several case-control epidemiology studies investigated the relationship between adverse pregnancy outcomes (spontaneous abortions and/or congenital malformations) and maternal exposure to solvents, including 1,1,1-trichloroethane (Lindbohm et al. 1990; Taskinen et al. 1989; Windham et al. 1991). No

clear evidence of a relationship between exposure to 1,1,1-trichloroethane and adverse pregnancy outcomes was found in any of these studies.

The potential developmental toxicity of inhaled 1,1,1-trichloroethane has been examined in rats and mice. Schwetz et al. (1975) exposed pregnant females of both species to moderate concentrations of 1,1,1-trichloroethane on days 6–15 of gestation. The only significant finding was an increase in absolute liver weight of maternal rats but not of maternal mice. Indices of embryo/fetotoxicity were comparable to controls. York et al. (1982) exposed female rats to 2,100 ppm of 1,1,1-trichloroethane for 2 weeks prior to mating and/or throughout pregnancy. There were no signs of maternal toxicity in any test group. A significant decrease in fetal body weight was observed in groups exposed either before and during pregnancy or during pregnancy only. Fetal body weights were not affected in the group exposed to 1,1,1-trichloroethane before pregnancy only. A significant increase in the incidence of delayed ossification and soft-tissue anomalies was observed only in the group that was exposed during both the premating period and gestation. Pup survival and weight gain were not affected by treatment, and neither was pup performance on neurobehavioral tests. There was no evidence of gross lesions upon necropsy at 12 months. Exposure of pregnant rats to 6,000 ppm of 1,1,1-trichloroethane during gestation days 6–15 decreased fetal weight and delayed ossification of the cervical centrum (BRRC 1987a). Signs of maternal toxicity at this concentration included hypoactivity during exposure, perioral wetness, decreased food consumption, and increased water consumption. Maternal toxicity may have contributed to the fetotoxicity observed. Maternal toxicity and fetotoxicity were not observed in rats exposed to 3,000 ppm. Pregnant rabbits exposed to 6,000 ppm of 1,1,1-trichloroethane during gestation days 6–18 had decreased weight gain during exposure (BRRC 1987b). A significant increase in the incidence of extra ribs was noted in the fetuses; however, this is an anomaly often associated with maternal toxicity, regardless of the test agent. No other evidence of embryotoxicity or teratogenicity was observed in this study.

Exposure of pregnant mice to 1,1,1-trichloroethane at a concentration of 2,000 ppm for 17 hours/day on gestation days 12–17 resulted in significantly reduced litter and postnatal pup weights, overt developmental delays (pinnae detachment, incisor eruption, eye opening), and impaired performance in behavioral tests (righting reflex, forelimb grip strength, negative geotaxis, inverted screen climbing) (Jones et al. 1996). There were no clinical signs of maternal toxicity and no statistically significant effects on number of litters, gestation length, litter size, number of live male or female pups per litter, or spontaneous motor activity, relative to controls. Other pregnant mice were exposed to 8,000 ppm 3 times/day for 60 minutes on gestation days 12–17 (Jones et al. 1996). Dams were nearly anesthetized

during exposure and exhibited mild tremors and gait abnormalities during observational battery testing. Significantly reduced postnatal pup weight, developmental delays (pinnae detachment, incisor eruption, eye opening), and impaired performance in behavioral tests (righting reflex, forelimb grip strength, negative geotaxis, rooting reflex) were noted. In a similar study of pregnant rats, exposed to 7,000 ppm of 1,1,1-trichloroethane 3 times per day for 60 minutes on gestation days 13–19, maternal weight gain was significantly reduced during the exposure period and dams exhibited clinical signs that included salivation, lacrimation, and abnormal gait (Coleman et al. 1999). Litters were completely resorbed in two of nine exposed dams and significant increases in gestation length were noted. Developmental effects included increased mortality at birth, decreased litter weight, and significant deficits in coordination, muscle strength, and spontaneous motor activity.

The highest NOAEL values and all reliable LOAEL values for developmental effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1. These data suggest that 1,1,1-trichloroethane is not a potent developmental toxin. Minor developmental effects characteristic of developmental delay were reported only at high doses and were usually accompanied by maternal toxicity.

3.2.1.7 Cancer

In case-control studies, occupational exposure to 1,1,1-trichloroethane was not found to be associated with astrocytic brain cancer (Heineman et al. 1994), renal cell carcinoma (Dosemeci et al. 1999), pancreatic cancer (Kernan et al. 1999), or esophageal or stomach cancer (Rohr Indus Inc. 1986, 1987). There was no significant correlation between release of 1,1,1-trichloroethane in 26 Florida counties in 1987 and age adjusted incidence of childhood brain tumors in these counties in 1992–1993 (Mulla 1996). Statistically significantly increased standardized incidence ratios for cancer of the nervous system and multiple myeloma were reported in male and female Finnish workers exposed to 1,1,1-trichloroethane (Anttila et al. 1995). However, the finding is based on only three cases of nervous system tumors and two cases of multiple myeloma, and most of the workers were exposed to other solvents as well. An increased risk of multiple myeloma was also observed in a cohort of female workers in Utah, but no association was found between non-Hodgkin's lymphoma and 1,1,1-trichloroethane exposure in these workers (Spirtas et al. 1991). The results, however, are questionable because only two cases of multiple myeloma were observed and the women were also exposed to many other chemicals. Based on the limited human data, it is not known whether inhaled 1,1,1-trichloroethane presents a human carcinogenicity concern.

A study of 1,1,1-trichloroethane vapor carcinogenicity in Fischer 344 rats and B6C3F1 mice was conducted by Quast et al. (1988). Animals were chronically exposed to moderate to high concentrations (150–1,500 ppm) of the chemical. In rats, no significant differences in survival were observed between groups. Body weights of treated and control rats were comparable except for a slight but significant decrease in high-dose females. Slight microscopic changes were seen in the livers of high-dose male and female rats at 6, 12, and 18 months, but these effects were not distinguishable from normal geriatric changes at 24 months. In mice, no significant differences in survival, growth, or incidence of nonneoplastic lesions were observed between groups. Pairwise comparisons between control and treated groups revealed no differences in the incidence of tumors in rats or mice. Two positive dose-related trends were statistically significant, but neither was considered treatment related. In male rats, a positive trend was evident for the incidence of benign bilateral interstitial cell tumors of the testes, a highly spontaneous tumor in the strain of rats tested. This trend disappeared when all interstitial cell tumors were combined and re-analyzed. A dose-related statistically significant trend was found for an increase in the combined incidence of benign adenomas and cystadenomas in the lacrimal gland of female mice, but the incidences were statistically comparable to concurrent controls as well as within the historical control range. The authors point out there was no increase in the incidence of lymphoreticular proliferative processes in either species in this study. This study adequately demonstrated no evidence of carcinogenicity by the inhalation route at the exposure levels used, which approach the maximum tolerated dose (MTD). An apparent increase in the occurrence of immunoblastic lymphosarcomas of the lung was reported in rats tested in an oral carcinogenicity study (Maltoni et al. 1986), described in Section 3.2.2.8.

3.2.2 Oral Exposure

3.2.2.1 Death

A single report of human oral exposure to 1,1,1-trichloroethane was found in the literature. A man survived after accidentally drinking a single . 600 mg/kg dose of 1,1,1-trichloroethane (Stewart and Andrews 1966). Clinical signs of toxicity were limited to a burning sensation in the throat, nausea, and incapacitating vomiting and diarrhea.

Torkelson et al. (1958) reported acute oral LD_{50} values of 12,300 and 10,300 mg/kg for male and female rats, respectively. LD_{50} values for other species include 11,240 mg/kg for mice, 9,470 mg/kg for guinea pigs, and 5,660 mg/kg for rabbits (Torkelson et al. 1958). A more recent study reported LD_{50} values of 17,148 and 12,996 mg/kg for male and female mice, respectively (Kinkead and Wolfe 1992). In 6-week studies, lethality was produced by gavage doses of 5,620 mg/kg/day in rats and 10,000 mg/kg/day in mice (NCI 1977). Repeated gavage doses of 2,500 mg/kg/day resulted in high rates of mortality within 50 days (Bruckner et al. 2001). Larger doses (≥5,000 mg/kg/day) for shorter time periods (11 days or less) were even more lethal (Bruckner et al. 2001). In chronic studies, effects on survival occurred at much lower doses. Survival decreased in rats exposed to 750 mg/kg/day and mice exposed to 2,807 mg/kg/day by gavage (NCI 1977). Chronic oral exposure to 500 mg/kg/day of 1,1,1-trichloroethane by gavage did not affect rat survival (Maltoni et al. 1986). Survival of rats and mice was not affected by administration of 1,1,1-trichloroethane in the diet at concentrations as high as 80,000 ppm (approximate doses as high as 5,000 and 23,000 mg/kg/day, respectively) for 13 weeks (NTP 2000).

Exposure to high oral doses of 1,1,1-trichloroethane can be lethal to animals and, presumably, to humans. The levels associated with decreased survival in animals appeared to decrease as exposure duration increased.

Reliable LD_{50} values and LOAEL values for death are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.2 Systemic Effects

The highest NOAEL values and all LOAEL values from each reliable study for each systemic effect in each species and duration are recorded in Table 3-2 and plotted in Figure 3-2.

No reports were located in which endocrine, ocular, or metabolic effects were associated with oral exposure of humans or animals to 1,1,1-trichloroethane.

Respiratory Effects. No studies were located regarding respiratory effects in humans after oral exposure to 1,1,1-trichloroethane.

Only one oral study investigated the respiratory effects of 1,1,1-trichloroethane in animals. Chronic oral exposure of rats to 1,500 mg/kg/day and mice to 5,615 mg/kg/day by gavage did not affect the incidence

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

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	ACUTE EXPOSURE						
	Death						
1	Rat (Sprague-Dawley)	Once (GO)		4000 M			Bruckner et al. 2001
2	Rat (Sprague-Dawley)	11 d d 1-5, 8-11 1x/d (GO)		500 M		5000 M (3/15 died)	Bruckner et al. 2001
3	Rat (Sprague-Dawley)	once (GO)				17148 M (LD50) 12996 F (LD50)	Kinkead and Wolfe 1992
4	Rat (NS)	once (G)				10300 F (LD50)	Torkelson et al. 1958
5	Mouse (NS)	once (G)				11240 (LD50)	Torkelson et al. 1958
6	Gn Pig (NS)	once (G)				9470 M (LD50)	Torkelson et al. 1958

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
7	Rabbit (NS)	once (G)				5660 F (LD50)	Torkelson et al. 1958
	Systemic						
8	Rat (Sprague-Dawley)	Once (GO)	Hepatic	4000 M			Bruckner et al. 2001
			Renal	4000 M			
			Bd Wt	4000 M			
9	Rat (Sprague-Dawley)	11 d d 1-5, 8-11 1x/d (GO)	Hepatic	10000 M			Bruckner et al. 2001
			Bd Wt	500 M	5000 M (14% reduced terminal body weight)		
10	Rat (NS)	7 d 1 x/d (GO)	Hepatic	1650			Platt and Cockrill 1969
			Bd Wt	1650			

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

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
11	Rat (Sprague-Dawley)	once (GO)	Hepatic		1330 M (ED50 for increased SGOT)		Tyson et al. 1983
12	Rat (Wistar)	1 d (GO)	Hepatic	1370 M			Vainio et al. 1976
	Neurological						
13	Human	once		600 M			Stewart and Andrews 1966
14	Rat (Sprague-Dawley)	11 d d 1-5, 8-11 1x/d (GO)		500 M		5000 M (hyperexcitability followed by narcosis)	Bruckner et al. 2001
15	Rat (Fischer 344)	4 d 1 x/d (GO)			705 F (altered EEG, FEP, and SEP)		Spencer et al. 1990

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

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	INTERMEDIATE EXPOSURE						
	Death						
16	Rat (Sprague-Dawley)	13 wk 5 d/wk 1 x/d 1x/d (GO)		500 M		2500 M (5/15 died)	Bruckner et al. 2001
17	Rat (Osborne-Mendel)	6 wk 5 d/wk (GO)				5620 F (2/10 died)	NCI 1977
18	Mouse (B6C3F1)	6 wk 5 d/wk (GO)				10000 (8/10 died)	NCI 1977
	Systemic						
19	Rat (Sprague-Dawley)	13 wk 5 d/wk 1 x/d 1x/d (GO)	Hepatic	500 M	2500 M (induction of serum liver enzymes)		Bruckner et al. 2001
			Bd Wt	500 M	2500 M (reduced body weight)		
20	Rat (Osborne-Mendel)	6 wk 5 d/wk (GO)	Bd Wt	3160	5620 F (unspecified decrease in body weight gain)		NCI 1977

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
21	Rat (F344/N)	Continuous 13 wk (F)	Hepatic	2500 F	5000 F (decreased absolute and relative liver weight)		NTP 2000
			Bd Wt	2400 M	4800 M (10% decreased final body weight)		
22	Mouse (B6C3F1)	6 wk 5 d/wk (GO)	Bd Wt	5620			NCI 1977
23	Mouse (B6C3F1)	Continuous 13 wk (F)	Bd Wt	1770 M[b] 2820 F	3500 M (>10% decreased terminal body weight, >20% depressed body weight gain) 5600 F (>10% decreased terminal body weight)		NTP 2000
	Neurological						
24	Rat (Sprague-Dawley)	13 wk 5 d/wk 1 x/d 1x/d (GO)		500 M		2500 M (hyperexcitability, narcosis)	Bruckner et al. 2001

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Reproductive						
25	Rat (Sprague-Dawley)	70 d ad libitum (W)		2.96 F			NTP 1988a; George et al. 1989
26	Rat (F344/N)	Continuous 13 wk (F)		2400 M	4800 M (10% reduction in epididymal spermatozoal concentration)		NTP 2000
27	Mouse (Swiss ICR)	25 wk ad libitum (W)		1000			Lane et al. 1982
28	Mouse (B6C3F1)	Continuous 13 wk (F)		15000 M 22900 F			NTP 2000
	Developmental						
29	Rat (Fischer- 344	Gd 6-21 Ld 1-10 (GO)		750			Dow Chemical 1993; Maurissen et al. 1994
30	Rat (CD)	70 d ad libitum (W)		3.5 F			NTP 1988a; George et al. 1989

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

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
31	Rat (Sprague-Dawley)	40 d ad libitum (W)		2.4 F			NTP 1988b
32	Mouse (Swiss ICR)	25 wk ad libitum (W)		1000			Lane et al. 1982
	CHRONIC EXPOSURE						
	Death						
33	Rat (Osborne-Mendel)	78 wk 5 d/wk (GO)				750 (survival decreased by approximately 50%)	NCI 1977
34	Mouse (B6C3F1)	78 wk 5 d/wk (GO)				2807 F (14% decreased survival)	NCI 1977
	Systemic						
35	Rat (Sprague-Dawley)	104 wk 4-5 d/wk (GO)	Bd Wt		500 F (body weight gain reduced 12% after 80 weeks)		Maltoni et al. 1986

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
36	Rat (Osborne-Mendel)	78 wk 5 d/wk (GO)	Resp	1500			NCI 1977
			Cardio	1500			
			Gastro	1500			
			Hemato	1500			
			Musc/skel	1500			
			Hepatic	1500			
			Renal	1500			
			Dermal	1500			
			Bd Wt		750 (significant reduction in body weight gain, but not quantified)		

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

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
37	Mouse (B6C3F1)	78 wk 5 d/wk (GO)	Resp	5615			NCI 1977
			Cardio	5615			
			Gastro	5615			
			Hemato	5615			
			Musc/skel	5615			
			Hepatic	5615			
			Renal	5615			
			Dermal	5615			
			Bd Wt		2807 (significant decrease in body weight gain, but not quantified)		
	Immuno/ Lymphoret						
38	Rat (Osborne-Mendel)	78 wk 5 d/wk (GO)		1500			NCI 1977

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
39	Mouse (B6C3F1)	78 wk 5 d/wk (GO)		5615			NCI 1977
	Neurological						
40	Rat (Osborne-Mendel)	78 wk 5 d/wk (GO)		1500			NCI 1977
41	Mouse (B6C3F1)	78 wk 5 d/wk (GO)		5615			NCI 1977
	Reproductive						
42	Rat (Osborne-Mendel)	78 wk 5 d/wk (GO)		1500			NCI 1977
43	Mouse (B6C3F1)	78 wk 5 d/wk (GO)		5615			NCI 1977

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

b Used to derive an intermediate-duration oral minimal risk level (MRL) of 20 mg/kg/day; daily ingested dose divided by an uncertainty factor of 100 (10 for extrapolation from mice to humans and 10 for human variability)

Bd wt = body weight; Cardio = cardiological; d = day(s); Derm = dermal; ED50 = effective dose, 50%; EEG = electroencephalogram; F = female; FEP = flash evoked potential; G = gavage- not specified; Gastro = gastrointestinal; Gd = gestation day; Gn Pig = guinea pig; GO = gavage in oil; Hemato = hematological; Ld = lactation day; LD50 = lethal dose; 50 kill; LOAEL = lowest-observed-adverse-effect level; M = male; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse effect level; resp = respiratory; SEP somatosensory evoked potential; SGOT = serum glutamate oxaloacetate transaminase; wk = week(s); x = time(s)

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

Acute (≤14 days)

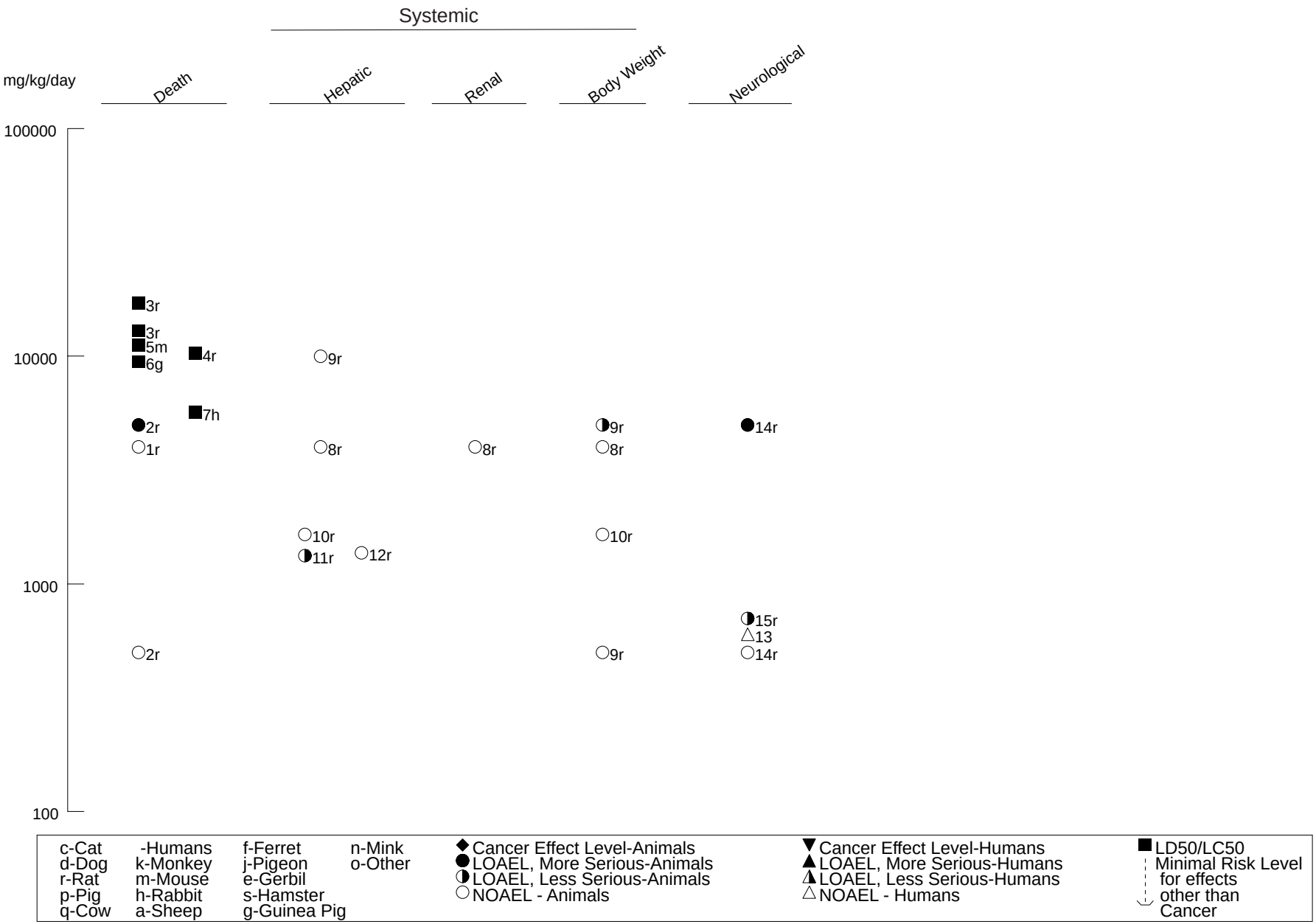


Figure 3-2. Levels of Significant Exposure to 1,1,1-Trichloroethane - Oral (*Continued*)

Intermediate (15-364 days)

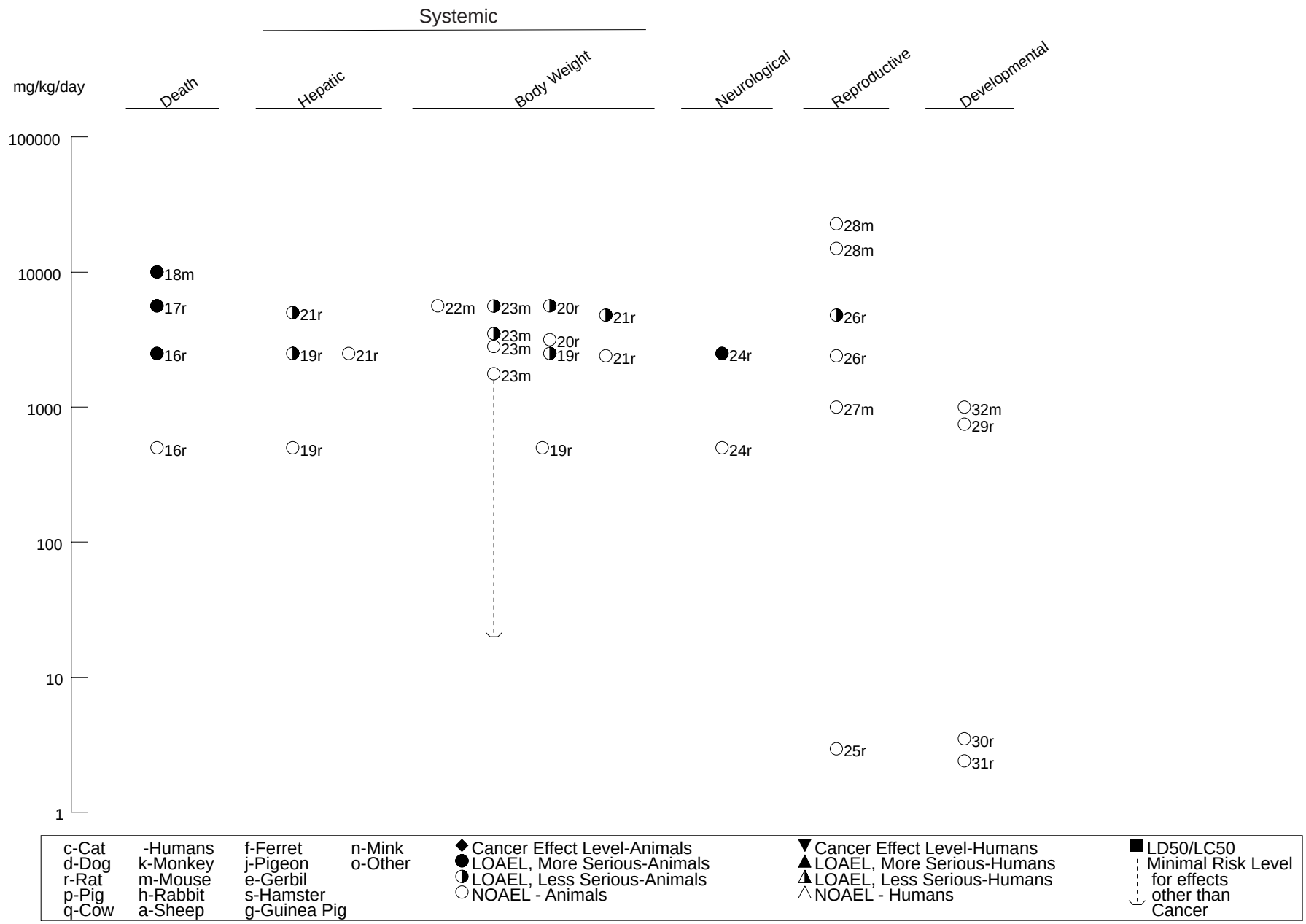
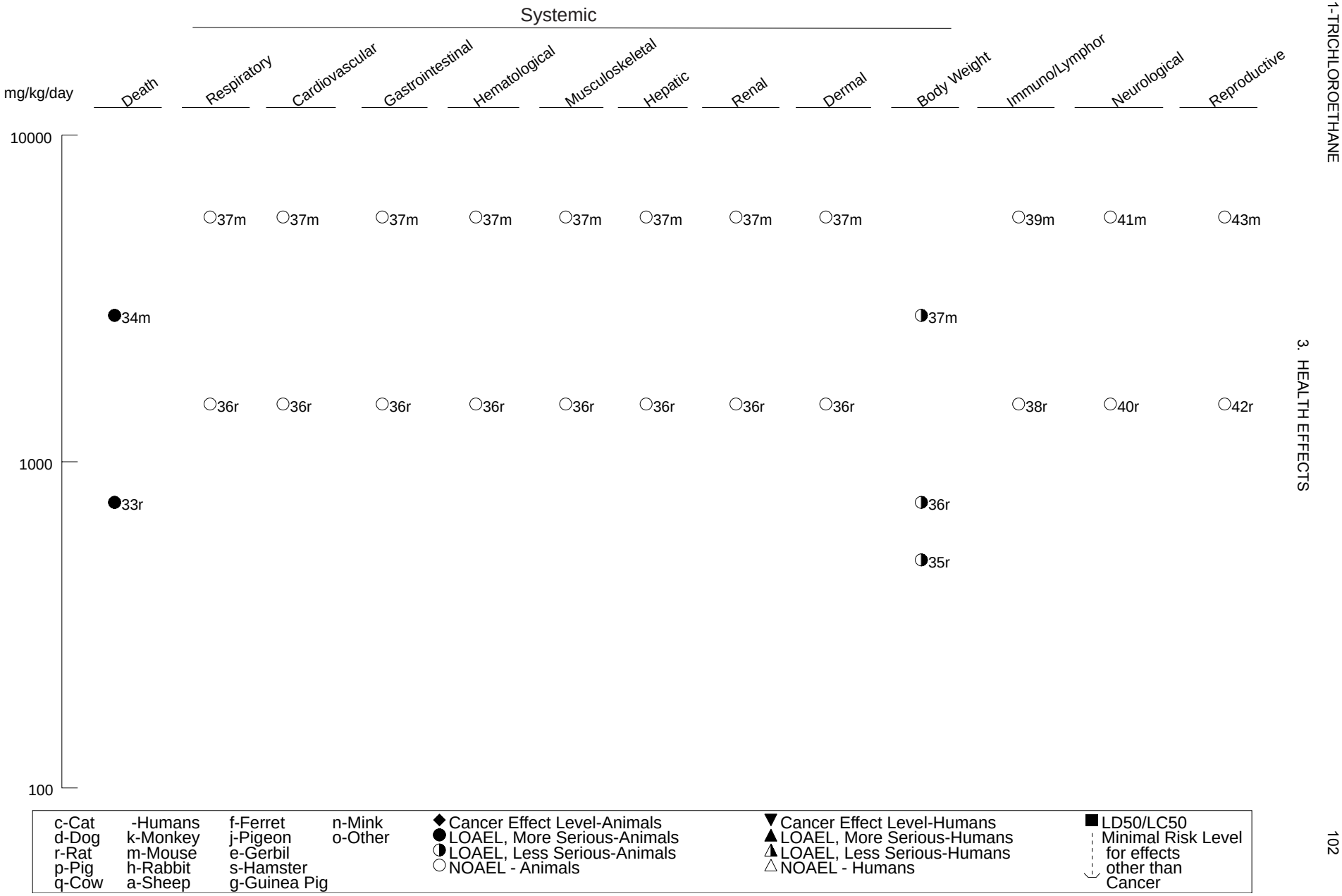


Figure 3-2. Levels of Significant Exposure to 1,1,1-Trichloroethane - Oral (*Continued*)

Chronic (≥365 days)



of lesions in the lungs, trachea, or nasal passages (NCI 1977). NOAEL values derived from this study are recorded in Table 3-2 and plotted in Figure 3-2. Based on the negative results in the NCI (1977) study and the generally negative results in inhalation studies in which respiratory tissues came into direct contact with high levels (see Section 3.2.1.2), 1,1,1-trichloroethane is not expected to produce respiratory effects following ingestion in humans.

Cardiovascular Effects. Electrocardiogram readings were normal 4 hours after a man accidentally drank a single 600 mg/kg dose of 1,1,1-trichloroethane (Stewart and Andrews 1966).

Cardiovascular effects of ingested 1,1,1-trichloroethane have been investigated only by histopathological examination of exposed animals. Chronic oral exposure of rats to 1,500 mg/kg/day and mice to 5,615 mg/kg/day did not affect the incidence of lesions in the heart (NCI 1977). NOAEL values derived from this study are recorded in Table 3-2 and plotted in Figure 3-2.

The usefulness of histopathological heart examinations is limited, considering the findings of serious effects on cardiovascular function without pathological lesions in animals after acute exposure to high levels of 1,1,1-trichloroethane via inhalation. Therefore, existing data are insufficient to assess cardiovascular effects from oral exposure to 1,1,1-trichloroethane.

Gastrointestinal Effects. Severe vomiting and diarrhea began 1 hour after ingestion and continued for 6 hours in a man who survived after accidentally drinking a single 600 mg/kg dose of 1,1,1-trichloroethane (Stewart and Andrews 1966). The patient reported feeling a burning sensation in his mouth and throat immediately after swallowing the dose.

Gastrointestinal effects of orally administered 1,1,1-trichloroethane were investigated only by histopathological examination in animals. Chronic oral exposure of rats to 1,500 mg/kg/day and mice to 5,615 mg/kg/day by gavage in oil did not affect the incidence of nonneoplastic lesions in the stomach, intestines, and pancreas (NCI 1977). NOAEL values derived from this study are recorded in Table 3-2 and plotted in Figure 3-2.

The results of the NCI (1977) study suggest that 1,1,1-trichloroethane does not produce gastrointestinal toxicity, while the case report of Stewart and Andrews (1966) shows that swallowing a large, undiluted dose of this chemical can produce severe gastrointestinal upset and some irritation of the throat.

Hematological Effects. Hematological parameters remained within normal limits in tests beginning 4 hours after exposure in a man who survived after accidentally drinking a single 600 mg/kg dose of 1,1,1-trichloroethane (Stewart and Andrews 1966).

Oral exposure of rats and mice to 1,1,1-trichloroethane in the diet at concentrations as high as 80,000 ppm (approximate doses as high as 5,000 and 23,000 mg/kg/day in rats and mice, respectively) did not result in apparent treatment-related hematological effects (NTP 2000). Chronic oral exposure of rats to 1,500 mg/kg/day and mice to 5,615 mg/kg/day by gavage in oil did not affect the incidence of nonneoplastic lesions in the bone marrow (NCI 1977). NOAEL values derived from this study are recorded in Table 3-2 and plotted in Figure 3-2.

The limited data available suggest that ingested 1,1,1-trichloroethane does not produce hematological effects.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after oral exposure to 1,1,1-trichloroethane.

Only one study investigated musculoskeletal effects in animals exposed to 1,1,1-trichloroethane orally. Chronic oral exposure of rats to 1,500 mg/kg/day and mice to 5,615 mg/kg/day by gavage in oil did not affect the incidence of nonneoplastic lesions in the muscles or bones (NCI 1977). NOAEL values derived from this study are recorded in Table 3-2 and plotted in Figure 3-2.

Hepatic Effects. Stewart and Andrews (1966) reported a case in which a man survived drinking 1 ounce (600 mg/kg) of 1,1,1-trichloroethane. Serum transaminase levels remained within normal limits, but serum bilirubin levels became slightly elevated after 48 hours. Increased serum bilirubin levels may result from reduced biliary excretion (i.e., cholestatic liver damage). Alternatively, hyperbilirubinemia may result from diminished hepatic conjugative metabolism of bilirubin.

Elevated SGOT levels, often seen in conjunction with hepatic damage and damage of other tissues, were reported in rats given a single oral dose of 1,330 mg/kg 1,1,1-trichloroethane (Tyson et al. 1983). Levels of SGPT, which is more specific for liver damage, remained unchanged in this study, however. Similar results in rats (little change in SGPT activity) were reported by others (Xia and Yu 1992). There were no

indications of 1,1,1-trichloroethane-induced liver damage in rats given a single gavage dose of 4,000 mg/kg/day or repeated gavage doses as high as 10,000 mg/kg/day (Bruckner et al. 2001). Data regarding the effect of 1,1,1-trichloroethane on the activity of rat liver enzymes are inconclusive. Increased liver microsomal and cytoplasmic protein content were found, although they were not accompanied by increases in activity of enzymes or increased liver weight (Platt and Cockrill 1969). Reduced levels of cytochrome P-450 and epoxide hydratase, suggesting inhibition of these enzymes, was reported in another study (Vainio et al. 1976). Bruckner et al. (2001) found some evidence in rats of enzyme induction at low doses and inhibition at high doses. In an intermediate-duration study, mild liver effects (small increases in SGPT and ornithine carbamyl transferase [OCT]) occurred at 5,000 mg/kg/day (Bruckner et al. 2001). Relative liver weight was increased by approximately 11% ($p<0.05$) in rats administered 1,1,1-trichloroethane by oral gavage for 21 days, but there were no histopathological signs of hepatotoxicity (NTP 1996). Decreased liver weights in female rats administered 80,000 ppm (5,000 mg/kg/day) of 1,1,1-trichloroethane in the diet for 13 weeks were attributed to reduced body weights, not adverse liver effects (NTP 2000). No liver effects were seen in similarly treated male rats, or in male or female mice receiving doses as high as 15,000 and 23,000 mg/kg/day, respectively. Chronic gavage administration of 1,1,1-trichloroethane did not affect the incidence of nonneoplastic lesions in the livers of rats or mice (NCI 1977). The highest NOAEL values and all reliable LOAEL values for hepatic effects in each species and exposure duration category are recorded in Table 3-2 and plotted in Figure 3-2.

Human and animal studies suggest that large amounts of ingested 1,1,1-trichloroethane may produce mild hepatotoxicity; however, whether 1,1,1-trichloroethane is an inducer or inhibitor of biotransformation enzymes following oral exposure is unclear.

Renal Effects. BUN levels were not elevated 4 hours after a man accidentally ingested a single 600 mg/kg dose of 1,1,1-trichloroethane (Stewart and Andrews 1966).

No effects on kidney weight or histology were found in rats given a single gavage dose of 4,000 mg/kg/day, repeated doses of 10,000 mg/kg/day, or intermediate-duration exposure to 5,000 mg/kg/day (Bruckner et al. 2001). There was a slight transient increase in BUN in the rats repeatedly given 10,000 mg/kg/day (Bruckner et al. 2001). Urinalysis performed on male rats administered 165 mg/kg/day of 1,1,1-trichloroethane by gavage for 21 days revealed significant increases in mean urinary protein and SGOT, but no histopathological evidence of renal damage (NTP 1996). The statistical significance of this finding is questionable since it was based on only four surviving rats. Male

rats administered ≥10,000 ppm (600 mg/kg/day) of 1,1,1-trichloroethane in the diet for 13 weeks exhibited kidney lesions indicative of hyaline droplet nephropathy (NTP 2000); this effect is specific to male rats and is not a human health concern. Chronic gavage exposure of rats to 1,500 mg/kg/day and mice to 5,615 mg/kg/day did not affect the incidence of nonneoplastic lesions in the kidneys (NCI 1977). NOAEL values derived from these studies are recorded in Table 3-2 and plotted in Figure 3-2.

Data from animals suggest that the kidney is not a target of 1,1,1-trichloroethane taken orally. Sensitive tests of renal function have not apparently been performed, however, in animals ingesting 1,1,1-trichloroethane.

Dermal Effects. No studies were located regarding dermal effects in humans after oral exposure to 1,1,1-trichloroethane.

Only one study investigated dermal effects following oral exposure in animals. Chronic oral exposure by gavage of rats to 1,500 mg/kg/day and mice to 5,615 mg/kg/day of 1,1,1-trichloroethane did not affect the incidence of nonneoplastic skin lesions (NCI 1977). NOAEL values derived from this study are recorded in Table 3-2 and plotted in Figure 3-2. The scarcity of data regarding dermal effects in humans or animals after oral exposure to 1,1,1-trichloroethane precludes assessing potential injury of this tissue.

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

Several studies monitored body weight in animals dosed orally with 1,1,1-trichloroethane. Reduced body weight gain was produced in rats by repeated doses ≥5,000 mg/kg/day in short-term studies and ≥2,500 mg/kg/day in intermediate-duration studies (Bruckner et al. 2001). Reduced body weight gain was noted in male (but not female) rats administered 1,1,1-trichloroethane in the diet at a concentration of 80,000 ppm (doses as high as 4,800 and 5,000 mg/kg/day in males and females, respectively) for 13 weeks (NTP 2000). In similarly treated male and female mice, reduced body weight gain was observed at 1,1,1-trichloroethane concentrations ≥5,000 and 10,000 ppm, respectively (doses of approximately 850 and 2,850 mg/kg/day, respectively) (NTP 2000). An intermediate-duration oral MRL of 18 mg/kg/day was derived for 1,1,1-trichloroethane based on the results of this study, as described in the footnote in Table 3-2. In another study, reduced body weight gain was reported at 5,620 mg/kg/day in rats exposed for 6 weeks and 750 mg/kg/day in rats exposed for 78 weeks (NCI 1977). Body weight gain

in rats was reduced by an even lower dose (500 mg/kg/day) in a second chronic study, but only after 80 weeks of exposure (Maltoni et al. 1986). In mice, 5,620 mg/kg/day did not affect body weight in a 6-week study, but 2,807 mg/kg/day was sufficient to reduce body weight gain in a 78-week study (NCI 1977). These limited data on the effects of orally administered 1,1,1-trichloroethane on body weight gain in animals suggest time- and dose-response relationships.

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

3.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans after oral exposure to 1,1,1-trichloroethane.

Immunological effects in animals were investigated only by histopathological examination of certain tissues. There was no effect on the incidence or type of nonneoplastic lesions in the thymus or spleen of rats or mice after chronic gavage exposure to high doses of 1,1,1-trichloroethane (NCI 1977). NOAEL values derived from this study are recorded in Table 3-2 and plotted in Figure 3-2. The scarcity of data pertaining to immunological effects in humans or animals after oral exposure to 1,1,1-trichloroethane precludes an assessment of immunotoxicity.

3.2.2.4 Neurological Effects

A thorough neurological examination (details not reported) found no abnormalities in a man who had ingested 600 mg/kg of 1,1,1-trichloroethane 4 hours earlier (Stewart and Andrews 1966).

Acute oral exposure of rats to 1,1,1-trichloroethane (705 mg/kg/day) did not result in behavior or appearance changes that could be detected after 2 days by a battery of observational measures, but did produce distinct neurophysiological alterations after 4 days. These alterations included marked changes in the flash-evoked potential (FEP) and electroencephalogram (EEG) recordings. Such effects are similar to those seen after inhalation exposure, and smaller changes in the somatosensory-evoked potential (SEP) (Spencer et al. 1990). No significant changes in tissue levels of monoamine neurotransmitters and metabolites were found in the brain of rats given single oral doses of 3,250 mg/kg of 1,1,1-trichloroethane

and sacrificed 2 hours later (Kanada et al. 1994). Rats given high oral doses of 1,1,1-trichloroethane (≥2,500 mg/kg/day) exhibited a short period of hyperactivity, followed by a period of prolonged narcosis after daily dosing in acute- and intermediate-duration studies (Bruckner et al. 2001). No clinical signs of neurotoxicity were seen in rats and mice receiving 1,1,1-trichloroethane in the diet at concentrations as high as 80,000 ppm (doses as high as 4,800 and 5,000 mg/kg/day in males and females, respectively) for 13 weeks (NTP 2000). Neurological effects were investigated by histopathological examination of the brain and nerves in a chronic study (NCI 1977). There was no effect on the incidence or type of lesions in the brain or nerves of rats or mice after chronic gavage exposure to 1,1,1-trichloroethane at doses as high as 1,500 and 5,615 mg/kg/day, respectively (NCI 1977). Failure to detect neural lesions by routine histopathology in this study does not rule out the occurrence of neurological effects following chronic oral exposure since physical changes in the brain did not accompany residual neurological effects seen in inhalation studies.

Reliable NOAEL and LOAEL values for neurological effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2. Limited information is available regarding the neurological effects of 1,1,1-trichloroethane following oral exposure, but the observation of narcosis in the studies by Bruckner et al. (2001) and the results of the acute neurophysiology study in rats suggest that the neurotoxicity of orally administered 1,1,1-trichloroethane may be similar to that observed following inhalation exposure.

3.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to 1,1,1-trichloroethane.

Limited information is available regarding reproductive effects in animals following oral exposure to 1,1,1-trichloroethane. A multigeneration reproduction study was conducted in mice by Lane et al. (1982). Male and female mice were exposed to 1,1,1-trichloroethane (1,000 mg/kg/day) in their drinking water. In the parental and F1 generations, exposure began prior to mating and was continued through gestation and lactation. Exposure usually precedes mating by the length of the sperm cycle in studies of this type, but the duration of premating exposure for the parental generation was abbreviated in this study. Treatment did not affect maternal survival, body weight, or reproductive performance. In another study, rats were exposed to 1,1,1-trichloroethane in the drinking water from before mating through lactation at

concentrations resulting in daily doses as high as 3 mg/kg (George et al. 1989; NTP 1988a). Maternal survival, body weight, fertility, and the duration of gestation were not affected. Reduced epididymal spermatozoal concentration was noted in male rats and mice administered 1,1,1-trichloroethane in the diet at a concentration of 80,000 ppm (approximate doses of 4,800 and 15,000 mg/kg/day) for 13 weeks, but there were no other indications of adverse male reproductive effects and no signs of altered estrus in similarly-treated female rats and mice (NTP 2000). In a chronic-duration study in rats and mice, there was no effect on the incidence or type of nonneoplastic lesions in the prostate, seminal vesicles, testes, or epididymis in males, or the uterus or ovary in females (NCI 1977).

The highest NOAEL values for reproductive effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2. There is limited evidence that oral exposure to high doses of 1,1,1-trichloroethane may influence sperm production in animals.

3.2.2.6 Developmental Effects

The possible relationship between developmental effects and exposure to 1,1,1-trichloroethane in the drinking water was investigated in a series of epidemiology studies (Deane et al. 1989; Wrensch et al. 1990a, 1990b). A leak in an underground storage tank resulted in contamination of well water with 1,1,1-trichloroethane and other chemicals. Levels of 1,1,1-trichloroethane were far higher than levels of other chemicals (1,700 ppb when first detected, reaching a maximum of 8,800 ppb after the well was closed). An excess of miscarriages and birth defects occurred in one exposed community but not in another. Hydrogeological modeling of water and contaminant distribution within the exposed communities showed that the leak was probably not responsible for the excessive adverse pregnancy outcomes in the one community, because estimated exposure to 1,1,1-trichloroethane was lower than in the other community. Average estimated exposure, in fact, was lower in areas reporting births with malformations than in those without. A related study, conducted on a larger scale, found an excess of major cardiac anomalies during the exposure period in the service area of the water company with the contaminated well, compared to the rest of the county (Santa Clara, California) (Swan et al. 1989). Detailed analysis of the temporal and spatial distribution of cases, however, did not support the hypothesis that contamination of the well produced these adverse effects. In a more recent report, no statistically significant effects were seen in a 3-year assessment of birth outcome among northern New Jersey residents of 75 towns where some water supplies were contaminated with 1,1,1-trichloroethane and other chemicals (Bove et al. 1995).

Lane et al. (1982) investigated the developmental effects of 1,1,1-trichloroethane in mice in a multigeneration reproduction study modified to allow screening for teratogenic and dominant lethal effects. Mice of either sex were exposed to 1,1,1-trichloroethane in their drinking water. Exposure for the initial test mice and the subsequent F1 generation began before mating and continued throughout gestation and lactation. Exposure is usually intended to precede mating by the length of the sperm cycle; however, in this study, the duration of premating exposure for the parental generation was abbreviated. No maternal toxicity was reported. There were no treatment-related embryotoxic or fetotoxic effects in either the F1 or F2 generation. Pup survival and body weight were also unaffected. There was no increase in the frequency of dominant lethal factors or in the incidence of skeletal or visceral malformations in either generation.

The developmental effects of 1,1,1-trichloroethane were also studied in rats (George et al. 1989; NTP 1988a, 1988b). Doses of up to 3 mg/kg/day of the chemical were administered in these studies to allow comparison with preliminary results of an earlier study (Dapson et al. 1984; Hutcheon et al. 1985) that reported increased incidences of cardiovascular anomalies at these doses. In the first study (NTP 1988a), 1,1,1-trichloroethane was added to the drinking water of male and female rats before mating and through lactation. Exposure to 1,1,1-trichloroethane had no effect on pup survival or body weight, or on the incidence of malformed pups. Particular attention was paid to developmental effects on the cardiovascular system. There was a high incidence of patent ductus arteriosus among pups that died on postnatal day 1 (10/28 exposed versus 0/8 control). Patent ductus arteriosus was found in only one treated pup (from the low-concentration group) sacrificed on postnatal day 4. No cardiovascular anomalies of any type were found in treated pups sacrificed on postnatal day 21, which was the time that Dapson et al. (1984) reported effects. The authors explain that patent ductus arteriosus is not unexpected in pups at the earlier time points (days 1 and 4), but do not address the apparent difference between treated and control groups on day 1. Most of the pups with patent ductus arteriosus were in the low-dose group; incidence was lower in the two higher-dose groups, and the effects were not statistically significant. These results suggest that 1,1,1-trichloroethane did not affect the development of patent ductus arteriosus in these rats.

In the second study (NTP 1988b), rats were exposed to 1,1,1-trichloroethane in the drinking water from premating through gestation at concentrations resulting in daily doses as high as 2.5 mg/kg. Dams were sacrificed on day 20 of gestation, and the fetuses were given comprehensive teratological examinations.

No embryotoxic or fetotoxic effects were reported. There was no effect on the incidence of external, visceral, or skeletal malformations. No cardiovascular abnormalities of any type were seen.

A study was designed to examine the neurobehavioral effects of 1,1,1-trichloroethane on the offspring of rats treated with the test material by gavage on gestation day 6 through lactation day 10 (Dow Chemical 1993; Maurissen et al. 1994). The doses used were 75, 250, and 750 mg 1,1,1-trichloroethane/kg/day. The end points examined included body weight, physical maturation landmarks, motor activity, functional observation battery, brain measurements and neuropathology, and evaluation of learning capacity, task performance, and short-term memory. Although sporadic differences between treated animals and controls were found with some tests, these were either not statistically significant or not dose-related, suggesting that the highest dose tested, 750 mg/kg/day, was a NOAEL for the study.

The highest NOAEL values for developmental effects in each species are recorded in Table 3-2 and plotted in Figure 3-2. The weight of evidence in experimental animal studies suggests that 1,1,1-trichloroethane is not a developmental toxicant when administered orally; however, this conclusion is limited by the use of low doses in some of the studies. Epidemiology studies found no evidence that exposure to 1,1,1-trichloroethane was responsible for the cluster of adverse pregnancy outcomes in Santa Clara County, California.

3.2.2.7 Cancer

Isacson et al. (1985) investigated the relationship between the presence of organic chemicals, including 1,1,1-trichloroethane, in drinking water and the incidence of cancer in Iowa residents. The authors contrasted towns that had detectable quantities of 1,1,1-trichloroethane in the water supply with those that did not and found no difference in the incidence of bladder, colon, lung, rectum, breast, or prostate cancer in people over 55 years of age. 1,1,1-Trichloroethane levels >0.1 µg/L (but unspecified) were detectable in this study. Assuming the average adult weighs 70 kg and drinks 2 liters of water per day, a concentration of 0.1 µg/L would produce a dose of approximately 0.000003 mg/kg/day. The authors concede that their data are not sensitive enough to support conclusions regarding the apparent lack of association between 1,1,1-trichloroethane in the water supply and cancer risk in humans. No other studies were located regarding risks of cancer in humans after oral exposure to 1,1,1-trichloroethane.

NCI (1977) conducted a bioassay for carcinogenicity of 1,1,1-trichloroethane in rats and mice. The test animals were exposed to high gavage doses of the chemical (750 or 1,500 mg/kg/day for rats and 2,807 or 5,615 mg/kg/day for mice) for 78 weeks. All animals were necropsied and the tissues were examined histologically. The incidence and type of neoplasms observed were similar to those seen in untreated controls. Vehicle controls were not used in this study. There was a significant dose-related decrease in survival of both rats and mice. Among rats, no males and only 2–4% females survived to the end of the experiment. Among mice, 22–30% of treated males and 26–46% of treated females survived. Because the high rate of early mortality may have lowered the incidence of late-appearing tumors, the authors did not consider this study an adequate test of 1,1,1-trichloroethane carcinogenicity in either species.

A screening-type study using only one gavage dose level (500 mg/kg/day for 104 weeks) and a less-than-optimal sample size (50 per sex in the vehicle controls, 40 per sex in the treatment group) reported an apparent increase in leukemia incidence in rats (Maltoni et al. 1986). Survival appeared comparable between control and treatment groups, but no statistical analysis was performed. Body weight was reduced in females after 80 weeks of the experiment. Although tumor incidences were not analyzed statistically, an apparent increase in the total incidence of rats with leukemias occurred, with 13/80 in treated rats and 4/100 in vehicle controls. The increase was due mainly to an increased incidence of immunoblastic lymphosarcomas in the lungs (seven in treated rats and one in controls). The biological and statistical significance of this finding cannot be determined because of the inherent limitations of the experimental design. The authors stated that, although definite conclusions could not be drawn based on this study, the results called for further experimentation to assess the carcinogenicity of 1,1,1-trichloroethane.

The inability to identify associations between human oral exposure and cancer incidence, as well as the limitations of the animal studies (i.e., high rate of early mortality, one dose level, small sample size), limit the assessment of potential carcinogenic effects in humans after oral exposure to 1,1,1-trichloroethane.

3.2.3 Dermal Exposure

Occupational exposure to 1,1,1-trichloroethane frequently involves both inhalation of and dermal contact with the chemical. There are many case reports of effects in individuals after occupational exposure to high levels of 1,1,1-trichloroethane, but inhalation appears to be the primary route of exposure in most of these cases. Although dermal exposure may have contributed to the effects observed, these cases are

discussed under Inhalation Exposure in Section 3.2.1. In a few cases, dermal exposure appeared to be more important, and these are discussed below. In all cases, except for superficial skin effects, any potential effect would likely be similar to inhalation effects at similar circulating blood levels.

3.2.3.1 Death

No studies were located regarding death in humans after dermal exposure to 1,1,1-trichloroethane.

Very high dose levels were required to cause death in animals after dermal exposure to 1,1,1-trichloroethane. Exposure to 15,800 mg/kg under a cuff killed <50% of the rabbits tested (Torkelson et al. 1958). Acute dermal exposure to lower doses did not cause death in rabbits or guinea pigs (Kinkead and Leahy 1987; Torkelson et al. 1958; Wahlberg and Boman 1979). Repeated-exposure studies employing doses up to 280 mg/kg/day (covered) or 500 mg/kg/day (uncovered) did not reveal any effect on mortality in rats or rabbits (Torkelson et al. 1958; Viola et al. 1981).

These limited data suggest that dermal exposure to 1,1,1-trichloroethane is lethal only at very high doses that could not be experienced under foreseeable circumstances. The LOAEL for death in acutely exposed rabbits is recorded in Table 3-3.

3.2.3.2 Systemic Effects

The highest NOAEL values and all LOAEL values from each reliable dermal study for each systemic effect in each species and duration are recorded in Table 3-3.

No reports were located in which musculoskeletal, endocrine, or metabolic effects were associated with oral exposure of humans or animals to 1,1,1-trichloroethane.

Respiratory Effects. No studies were located regarding respiratory effects in humans after dermal exposure to 1,1,1-trichloroethane.

Respiratory effects in animals were investigated by pathological examination of the lungs in one study. Dermal exposure for 90 days to 500 mg/kg/day of 1,1,1-trichloroethane (uncovered) had no effect on lung

Table 3-3 Levels of Significant Exposure to 1,1,1-Trichloroethane - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL				Reference Chemical Form
				Less Serious		Serious		
ACUTE EXPOSURE								
Death								
Rabbit (NS)	1 d 24 hr/d					15800 mg/kg/day	(under 50% mortality)	Torkelson et al. 1958
Systemic								
Human	1 d 5 min/d	Dermal		30 M mg/kg/day	(mild erythema)			Wahlberg 1984a
Human	10 d 1 x/d	Dermal	2 mg/kg/day					Wahlberg 1984b
Gn Pig (NS)	1 d 1/4 - 16 hr/d	Dermal		1300 mg/kg/day	(epidermal degeneration)			Kronevi et al. 1981
Gn Pig (NS)	10 d 1x/d	Dermal		220 mg/kg/day	(edema at application site)			Wahlberg 1984b
Gn Pig (NS)	1 d	Bd Wt				7360 mg/kg/day	(30% reduction in body weight gain)	Wahlberg and Boman 1979

Table 3-3 Levels of Significant Exposure to 1,1,1-Trichloroethane - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL			Reference Chemical Form
				Less Serious		Serious	
Rabbit (New Zealand)	1 d 24 hr/d	Bd Wt	2680 M mg/kg/day				Kinkead and Leahy 1987
Rabbit (NS)	1 d	Ocular	50 mg/kg/day				Marzulli and Ruggles 1973
Rabbit (NS)	10 d 1x/d	Dermal		35 mg/kg/day	(edema at application site)		Wahlberg 1984b

Table 3-3 Levels of Significant Exposure to 1,1,1-Trichloroethane - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form
INTERMEDIATE EXPOSURE						
Systemic						
Rat (Wistar)	22 d 16 x	Gastro	280 M mg/kg/day			Viola et al. 1981
		Hepatic		280 M mg/kg/day (increased SGOT, OCT, GGT; hepatocellular damage)		
		Renal	280 M mg/kg/day			
		Bd Wt			280 M mg/kg/day (60% decrease in body weight gain)	

Table 3-3 Levels of Significant Exposure to 1,1,1-Trichloroethane - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL		Reference Chemical Form
				Less Serious	Serious	
Rabbit (NS)	90 d 5 d/wk	Resp	500 M mg/kg/day			Torkelson et al. 1958
		Cardio	500 M mg/kg/day			
		Gastro	500 M mg/kg/day			
		Hemato	500 M mg/kg/day			
		Hepatic	500 M mg/kg/day			
		Renal	500 M mg/kg/day			
		Dermal		15 M mg/kg/day (mild skin irritation)		
		Bd Wt	500 mg/kg/day			
Immuno/ Lymphoret						
Rabbit (NS)	90 d 5 d/wk		500 M mg/kg/day			Torkelson et al. 1958
Neurological						
Rabbit (NS)	90 d 5 d/wk		500 F mg/kg/day			Torkelson et al. 1958

Table 3-3 Levels of Significant Exposure to 1,1,1-Trichloroethane - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL		Reference Chemical Form
				Less Serious	Serious	
Reproductive						
Rabbit (NS)	90 d 5 d/wk		500 M mg/kg/day			Torkelson et al. 1958

Bd wt = body weight; Cardio = cardiological; d = day(s); Derm = dermal; Gastro = gastrointestinal; GGT = gamma-glutalmyl transferase; NOAEL = no-observed-adverse effect level; NS = not specified; resp = respiratory; SGOT = serum glutamate oxaloacetate transaminase; wk = week(s); x = time(s)

weight or the incidence of gross or microscopic lung lesions in rabbits (Torkelson et al. 1958). A NOAEL derived from this study is recorded in Table 3-3.

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans after dermal exposure to 1,1,1-trichloroethane.

Cardiovascular effects in animals were investigated by histopathological examination in one study. Intermittent 90-day dermal exposure to 500 mg/kg/day of 1,1,1-trichloroethane (uncovered) had no effect on heart weight or the incidence of heart lesions in rabbits (Torkelson et al. 1958). A NOAEL derived from this study is recorded in Table 3-3. Much higher doses may be required to produce effects by the dermal route; high vapor concentrations were required to produce cardiotoxic effects by inhalation exposure (see Section 3.2.1.2), and percutaneous absorption of 1,1,1-trichloroethane is much slower and less complete than pulmonary absorption.

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after dermal exposure to 1,1,1-trichloroethane.

Gastrointestinal effects were not seen in animals dermally exposed to 1,1,1-trichloroethane. Rats exposed to 280 mg/kg/day of 1,1,1-trichloroethane under an occlusive dressing for 3 weeks showed no evidence of pancreatic damage, as determined by histopathological examination and serum lipase and amylase levels (Viola et al. 1981). Rabbits exposed to 500 mg/kg/day without occlusion for 90 days had no gross or microscopic lesions in the stomach or intestines (Torkelson et al. 1958).

These limited animal data suggest that dermal exposure to 1,1,1-trichloroethane will not result in gastrointestinal effects in humans. The NOAEL values for gastrointestinal effects in rats and rabbits are recorded in Table 3-3.

Hematological Effects. No studies were located regarding hematological effects in humans after dermal exposure to 1,1,1-trichloroethane.

One study of hematological effects in dermally-exposed animals was located. Hematological parameters, including red blood cell count, white blood cell count, and hemoglobin, were unaffected by dermal exposure to 500 mg/kg/day of 1,1,1-trichloroethane (uncovered) for 90 days in rabbits (Torkelson et al.

1958). A NOAEL derived from this study is recorded in Table 3-3. The scarcity of human and animal data limits the assessment of hematological effects that may be caused by dermal exposure to 1,1,1-trichloroethane.

Hepatic Effects. No studies were located regarding hepatic effects in humans after dermal exposure to 1,1,1-trichloroethane.

Mild hepatic effects have been reported in animals after dermal exposure to 1,1,1-trichloroethane. Levels of SGOT, ornithine carbamyl transferase, and gamma-glutamyl transferase, enzymes released into the serum from damaged hepatocytes, were significantly increased in rats dermally exposed to 280 mg/kg/day of 1,1,1-trichloroethane under occlusion in a 3-week study (Viola et al. 1981). Levels of SGPT, another indicator of hepatic damage, were not affected. Histopathological effects, including damage to hepatocytes (fatty degeneration and mitochondrial swelling) and the presence of small focal intralobular inflammatory infiltrates, were seen in the exposed rats. A study in which rabbits were dermally exposed to higher doses of 1,1,1-trichloroethane for a longer period (but without occlusion) did not reveal histopathological effects in the liver or changes in liver weight (Torkelson et al. 1958).

Animal data suggest that dermal exposure to high doses of 1,1,1-trichloroethane may result in liver effects. Although too little information exists to allow a detailed evaluation, skin absorption is not likely to be a problem for foreseeable exposures. The NOAEL and LOAEL values for hepatic effects are recorded in Table 3-3.

Renal Effects. No studies were located regarding renal effects in humans after dermal exposure to 1,1,1-trichloroethane.

Renal effects were investigated in two animal studies. Histopathological examination of the kidneys found no lesions following repeated dermal exposure to 280 mg/kg/day (covered) in rats or 500 mg/kg/day (uncovered) in rabbits (Torkelson et al. 1958; Viola et al. 1981).

The scarcity of human and animal data limits the assessment of renal effects that may be caused by dermal exposure to 1,1,1-trichloroethane. The NOAEL values for renal effects in rats and rabbits are recorded in Table 3-3.

Dermal Effects. Dermal exposure to 1,1,1-trichloroethane causes reversible effects in humans, which increase from mild irritation to chemical burns as exposure duration increases. Volunteers who immersed their thumbs in beakers of undiluted 1,1,1-trichloroethane for 30 minutes reported mild burning pain after . 10 minutes of exposure (Stewart and Dodd 1964). Following exposure, mild erythema and fine scaling were visible on the thumb. The scaling was easily rinsed and the erythema disappeared within 1 hour. Similar results were obtained when the entire hand was immersed in the beaker, except that the burning sensation began earlier, became more intense, and then was replaced by a feeling of cold that continued 10 minutes after exposure ended. When the subject repeatedly alternated immersion in 1,1,1-trichloroethane with exposure to air, intense cold was produced by evaporation of 1,1,1-trichloroethane from the skin. The hand remained cold for 45 minutes after the end of exposure.

Brief dermal exposure to a small amount of 1,1,1-trichloroethane covered with a glass disk produced an immediate increase in blood flow that dropped back to pre-exposure levels after 1 hour (Wahlberg 1984a). Slight, transient erythema was visible from 10 to 20 minutes following exposure. The subject reported mild stinging and burning sensations. None of these effects were found when a smaller amount of 1,1,1-trichloroethane was allowed to spread freely on the subject's skin, probably due to rapid evaporation of the chemical (Wahlberg 1984a). Repeated uncovered application of a small amount had no effect on skin-fold thickness and produced no visible dermal reaction (Wahlberg 1984b).

One case of allergic contact dermatitis from 1,1,1-trichloroethane was located in the literature (Ingber 1991). A worker whose job included using 1,1,1-trichloroethane to clean metal plates developed severe acute hand eczema soon after starting the job. The eczema persisted throughout 3 years of employment. Patch tests at that time showed a positive reaction to 1,1,1-trichloroethane. The eczema disappeared after a few weeks when contact with 1,1,1-trichloroethane was avoided. The possibility of the allergic reaction to being caused by 1,1,1-trichloroethane stabilizer was not discussed.

Assessments of the skin irritancy of 1,1,1-trichloroethane in animals reveal slight to moderate reactions. Based on single-application studies in rabbits, 1,1,1-trichloroethane was ranked as a moderate skin irritant by Duprat et al. (1976). A single application of 1,1,1-trichloroethane to the mouse ear resulted in significantly increased ear thickness approximately 1 hour following treatment (Iyadomi et al. 2000). Torkelson et al. (1958), however, reported only slight reddening and scaliness of rabbits' skin following a single application. Irritation observed following repeated application of the compound for 10 days was only slightly more noticeable and quickly disappeared after the end of treatment (Torkelson et al. 1958).

Skin-fold thickness increased 41–81% in rabbits and guinea pigs exposed repeatedly to dermal applications of 1,1,1-trichloroethane, and visible erythema and edema were present within 24–72 hours of the original exposure (Wahlberg 1984b). Intermediate-duration exposure to doses ranging from 15 to 500 mg/kg/day produced only slight, reversible irritation at the application site (Torkelson et al. 1958). Lack of dose and exposure methodology information makes it difficult to compare the results of these studies, but the weight of evidence suggests that 1,1,1-trichloroethane is not a strong dermal irritant in animals.

Kronevi et al. (1981) studied cellular changes produced in the intact skin of guinea pigs by exposure to 1 mL of undiluted 1,1,1-trichloroethane under a cover glass for durations ranging from 15 minutes to 16 hours. No gross effects were observed, indicating that the overall irritation produced was minor, but a host of degenerative changes in the epidermis, including karyopyknosis, karyolysis, perinuclear edema, and spongiosis, was found by histological examination. Focal junctional separation and cellular infiltration were observed in the upper part of the dermis. Effects were seen within 15 minutes of exposure, and some were still evident 16 hours later.

Exposure to 4,000 ppm 1,1,1-trichloroethane in the air for 4 hours caused the fur coat of mice to become dull (Evans and Balster 1993). This effect was most likely caused by direct contact of the chemical with the skin (see also Section 3.2.1.2).

Although extended dermal contact with relatively concentrated 1,1,1-trichloroethane may cause irritation and burning sensations of the skin of humans, most evidence in humans and animals indicates that this compound is not a strong skin irritant. There is one report of a 1,1,1-trichloroethane formulation acting as a skin sensitizer in humans. The highest NOAEL values and all reliable LOAEL values for dermal effects in each species and duration category are recorded in Table 3-3.

Ocular Effects. Individuals briefly exposed to high 1,1,1-trichloroethane vapor concentrations reported mild eye irritation (Stewart et al. 1961). This effect was most likely due to direct contact of the chemical with the eye.

Ocular administration of 1,1,1-trichloroethane caused only mild eye irritation in rabbits (Duprat et al. 1976; Krantz et al. 1959; Marzulli and Ruggles 1973; Torkelson et al. 1958). The study by Marzulli and

Ruggles (1973) was a survey in which 10 laboratories conducted the Draize eye test in rabbits using 1,1,1-trichloroethane and reported little or no eye irritation.

Although eye irritation produced by direct application of 1,1,1-trichloroethane seems to be minor, mice exposed continuously to 4,000 ppm 1,1,1-trichloroethane in the air for 4 hours exhibited eye irritation during exposure (Evans and Balster 1993). The highest NOAEL values and all reliable LOAEL values for ocular effects in each species and duration category are recorded in Table 3-3.

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

Animal studies have investigated the effect of topical 1,1,1-trichloroethane application on body weight. Acute exposure to 7,360 mg/kg of 1,1,1-trichloroethane (covered) decreased body weight gain in guinea pigs (Wahlberg and Boman 1979). A lower dose had no effect on body weight in rabbits (Kinkead and Leahy 1987). Intermediate exposure to 280 mg/kg/day under occlusion reduced growth in rats (Viola et al. 1981). Exposure to a higher dose for a longer period did not affect rabbit body growth, but 1,1,1-trichloroethane was applied uncovered in this study (Torkelson et al. 1958). Food consumption was not monitored in these studies. Effects of 1,1,1-trichloroethane on body weight may have been produced by effects on appetite and food intake secondary to central nervous system depression, rather than physiological effects on growth and development.

The scarcity of human and animal data limits the assessment of body weight effects caused by dermal exposure to 1,1,1-trichloroethane. The NOAEL and LOAEL values for body weight changes are recorded in Table 3-3.

3.2.3.3 Immunological and Lymphoreticular Effects

One report of a worker who developed allergic contact dermatitis to a formulation of 1,1,1-trichloroethane (Ingber 1991) is discussed in more detail under Dermal Effects in Section 3.2.3.2.

In animals, immunological effects following dermal exposure were investigated only by histopathological examination. No lesions or weight changes were found in the spleens of rabbits exposed to moderate 1,1,1-trichloroethane levels (500 mg/kg/day; no occlusion) in a 90-day study (Torkelson et al. 1958). The

NOAEL value derived from this study is recorded in Table 3-3. The scarcity of human and animal data precludes the assessment of potential effects on immune system tissues and function after dermal exposure to 1,1,1-trichloroethane.

3.2.3.4 Neurological Effects

Three women developed peripheral neuropathy after frequent, prolonged dermal contact with formulations of 1,1,1-trichloroethane and other chemicals at their workplace (Howse et al. 1989; Liss 1988). The women initially complained of numbness in their limbs, and subsequent nerve conduction studies showed alterations in peripheral nerve activity. The effect was diagnosed as primarily a distal sensory peripheral neuropathy. These cases were unusual because the effect was greater in the hands than in the feet, the reverse of most peripheral neuropathies. Sural nerve biopsies in two of the women performed 3–4 years after diagnosis revealed chronic neuropathy (axonopathy and myelinopathy) (Liss 1988). The authors did not establish a causal relationship with 1,1,1-trichloroethane. Two more recent cases of peripheral neuropathy were reported following exposure to 1,1,1-trichloroethane used as a degreasing agent (House et al. 1994, 1996).

Dermal studies including tests of neurological function in animals were not located. Neurological effects were investigated by histopathological examination of the brain in one study. The value of these data is limited, however, since physical changes in the brain have not been found to accompany serious neurological effects in high level inhalation studies. No lesions or weight changes were found in the brains of rabbits exposed to 500 mg/kg/day of 1,1,1-trichloroethane (no occlusion) in a study of intermediate duration (Torkelson et al. 1958). The NOAEL value derived from this study is recorded in Table 3-3. These data are not sufficient for assessing the neurotoxicity of 1,1,1-trichloroethane after dermal exposure to the compound.

3.2.3.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after dermal exposure to 1,1,1-trichloroethane.

Reproductive effects following dermal exposure were investigated only by histopathological examination in animals. No lesions or weight changes were found in the testes of rabbits exposed to 500 mg/kg/day of

1,1,1-trichloroethane (no occlusion) in a study of intermediate duration (Torkelson et al. 1958). The NOAEL value derived from this study is recorded in Table 3-3. The absence of human data, tests in female laboratory animals, and evaluation of reproductive function prevents an acceptable assessment of possible reproductive effects from dermally administered 1,1,1-trichloroethane.

3.2.3.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals after dermal exposure to 1,1,1-trichloroethane.

3.2.3.7 Cancer

No studies were located regarding cancer in humans or animals after dermal exposure to 1,1,1-trichloroethane.

3.3 GENOTOXICITY

The genotoxic effects of 1,1,1-trichloroethane have been studied extensively. The results are summarized in Tables 3-4 and 3-5. Although most tests of mutagenicity in the Ames *Salmonella* assay produced negative results, those conducted in a desiccator, to minimize evaporation and maximize exposure, were mostly positive (Gocke et al. 1981; Nestmann et al. 1980, 1984; Simmon et al. 1977). These results indicate that 1,1,1-trichloroethane may be mutagenic in *Salmonella*. The results were negative in other tests of genotoxicity in bacteria and fungi (see Table 3-5). 1,1,1-Trichloroethane is a relatively volatile compound; therefore, a high evaporation rate could result in lower doses reaching the microorganisms and thus affect the outcome of genotoxicity tests. This explanation may account for the largely negative results observed in tests with bacteria and fungi. On the other hand, many compounds more volatile than 1,1,1-trichloroethane are positive in these studies. A weakly positive result was obtained in a test for induction of deletions via intrachromosomal recombination in the yeast *Saccharomyces cerevisiae* (Brennan and Schiestl 1998).

Most assays of genotoxicity in mammalian cells have been negative, but 1,1,1-trichloroethane did produce chromosomal aberrations in Chinese hamster ovary cells *in vitro* (Galloway et al. 1987). *In vivo*

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

Species (test system)	End point	Results	Reference
Tradescantia	Pigmentation change in plant stamen hairs	+	Schairer et al. 1983
Allium	Chromosomal aberrations	+	Rank and Nelson 1994
Drosophila melanogaster	Sex linked recessive lethal mutations	–	Gocke et al. 1981
Drosophila melanogaster	Mitotic recombination	–	Vogel and Nivard 1993
Mouse erythrocytes	Micronucleus test	–	Tsuchimoto and Matter 1981
Mouse bone marrow	Micronucleus test	–	Gocke et al. 1981; Katz et al. 1981; Mackay 1990; Salamone et al. 1981
Mouse liver	DNA adducts	(+)	Turina et al. 1986
Mouse liver	DNA unwinding	–	Taningher et al. 1991

– = negative; + = positive; (+) = weakly positive; DNA = deoxyribonucleic acid

Table 3-5. Genotoxicity of 1,1,1-Trichloroethane *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Prokaryotic organisms:				
Salmonella typhimurium on plates	Reverse mutation	–	–	Baker and Bonin 1981; Brooks and Dean 1981; Ichinotsubo et al. 1981b; Legault et al. 1994; MacDonald 1981; Martire et al. 1981; Mersch-Sundermann 1989; Nagao and Takahashi 1981; Nestmann et al. 1980; Quillardet et al. 1985; Richold and Jones 1981; Rowland and Severn 1981; Simmon and Shepherd 1981; Trueman 1981; Venitt and Crofton-Sleigh 1981
S. typhimurium in liquid	Reverse mutation	–	–	Falck et al. 1985; Suovaniemi et al. 1985
S. typhimurium on plates in dessicator	Reverse mutation	+	+	Nestmann et al. 1980, 1984; Gocke et al. 1981; Simmon et al. 1977
		–	–	Milman et al. 1988
S. typhimurium	Fluctuation	–	–	Gatehouse 1981; Hubbard et al. 1981
S. typhimurium	Forward mutation	–	No data	Skopek et al. 1981
		–	–	Roldan-Arjona et al. 1991
S. typhimurium	*umu*-test	–	–	Nakamura et al. 1987; Ono et al. 1991a, 1991b
	Rec-assay for DNA repair	–	–	Kada 1981
Escherichia coli	Reverse mutation	–	–	Matsushima et al. 1981
E. coli	Differential killing	–	–	Green 1981; Tweats 1981
E. coli	Lambda prophage induction	–	–	Thomson 1981
E. coli	Gene induction	–	No data	Quillardet et al. 1985
E. coli	Growth inhibition	(+)	–	Rosenkranz et al. 1981
E. coli	DNA damage	No data	–	Legault et al. 1994
Vibrio fischeri	DNA damage	No data	–	Legault et al. 1994
Eukaryotic organisms:				
Fungi:				
Schizosaccharo-myces pombe	Forward mutation	–	–	Loprieno 1981
Aspergillus nidulans	Forward mutation	No data	–	Crebelli and Carere 1987

Table 3-5. Genotoxicity of 1,1,1-Trichloroethane *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
A. nidulans	Mitotic aneuploidy	No data	–	Cerebelli and Carere 1987; Crebelli et al. 1988
A. nidulans	Mitotic crossing over	No data	–	Crebelli and Carere 1987
Saccharomyces cerevisiae	Reversion	–	–	Mehta and von Borstel 1981
S. cerevisiae	Mitotic aneuploidy	No data	–	Whittaker et al. 1990
		–	No data	Parry and Sharp 1981
S. cerevisiae	Mitotic crossing over	–	–	Kassinova et al. 1981
S. cerevisiae	DNA repair	–	–	Sharp and Parry 1981a
S. cerevisiae	Mitotic gene conversion	–	–	Jagannath et al. 1981; Sharp and Parry 1981b; Zimmerman and Scheel 1981
S. cerevisiae	Gene deletions	No data	(+)	Brennan and Schiestl 1998
Mammalian cells:				
HeLa cells	Unscheduled DNA synthesis	–	–	Martin and McDermid 1981
Mouse hepatocytes	Unscheduled DNA synthesis	No data	+	Milman et al. 1988
Rat hepatocytes	Unscheduled DNA synthesis	No data	–	Althaus et al. 1982; Milman et al.1988; Shimada et al. 1985; Williams et al. 1989
Rat hepatocytes	Degranulation of endoplasmic reticulum	No data	+	Fey et al. 1981
Human lymphoblasts	Gene locus mutation	No data	–	Penman and Crespi 1987
L5178Y mouse lymphoma cells	Forward mutation	?	–	Myhr and Caspary 1988
		–	–	Mitchell et al. 1988b
Chinese hamster ovary cells	Chromosome aberrations	(+)	+	Galloway et al. 1987
Chinese hamster ovary cells	Sister chromatid exchange	–		Perry and Thomson 1981
		?	–	Galloway et al. 1987
Human peripheral lymphocytes	Sister chromatid exchange	No data	–	Lindahl-Kiessling et al. 1989
Baby hamster kidney cells	Cell transformation	–	No data	Styles 1981
		+	+	Daniel and Dehnel 1981

Table 3-5. Genotoxicity of 1,1,1-Trichloroethane *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Rat embryo cells F1706	Cell transformation	No data	+	Price et al. 1978
Hamster embryo cells	Cell transformation	No data	+	Hatch et al. 1982, 1983
Mice BALB/c-3T3 cells	Cell transformation	No data	+	Milman et al. 1988 Tu et al. 1985;
Calf thymus	Binding to DNA	–	No data	DiRenzo et al. 1982

– = negative; + = positive; (+) = weakly positive; ? = equivocal; DNA = deoxyribonucleic acid

micronucleus tests for chromosomal aberrations were all negative (Gocke et al. 1981; Katz et al. 1981; Halogenated Solvents Industry Alliance 1990; Salamone et al. 1981; Tsuchimoto and Matter 1981). Positive or weakly positive results were reported in assays for unscheduled DNA synthesis in mouse hepatocytes (Milman et al. 1988); degranulation of endoplasmic reticulum, which measures the ability of a compound to displace polysomes from endoplasmic reticulum in rat hepatocytes *in vitro* (Fey et al. 1981); and formation of DNA adducts (binding of the compound to DNA) in mouse liver *in vivo* (Turina et al. 1986). Tests of cell transformation in rat embryo cells, hamster embryo cells, baby hamster kidney cells, and mouse BALB/c-3T3 cells were almost all positive (Daniel and Dehnel 1981; Hatch et al. 1982, 1983; Milman et al. 1988; Price et al. 1978; Tu et al. 1985). Cell transformation systems are believed to be similar to the process of neoplastic transformation *in vivo*.

In summary, the existing genotoxicity data are largely negative, although 1,1,1-trichloroethane was mutagenic in a few assays with *Salmonella*, induced chromosomal aberrations in a Chinese hamster ovary cell assay, and was positive in most mammalian cell transformation assays.. In addition, positive results may have been produced by stabilizers and not 1,1,1-trichloroethane itself. Therefore, a firm conclusion regarding the genotoxic potential of 1,1,1-trichloroethane in humans is not possible.

3.4 TOXICOKINETICS

Upon first exposure, 1,1,1-trichloroethane is rapidly and efficiently absorbed by the lung, skin (under conditions to prevent evaporation), and gastrointestinal tract of humans and animals. As the duration of inhalation exposure increases, the percentage of absorption decreases because steady-state levels are approached in the blood and tissues, and 1,1,1-trichloroethane is metabolized at a low rate. Animal studies have demonstrated that, once absorbed, 1,1,1-trichloroethane is distributed by the blood to tissues and organs throughout the body, including to developing fetuses, with preferential distribution to fatty tissues. The predominant pathway of elimination of 1,1,1-trichloroethane in humans and animals, regardless of route of exposure, is exhalation of the unchanged compound. When exposure ceases, the compound is rapidly cleared from the body. In animal studies, only trace amounts of the compound remain in tissues within days of the termination of short-term exposure.

1,1,1-Trichloroethane is metabolized oxidatively, at low rates, to trichloroethanol and trichloroacetic acid by the cytochrome P-450 mixed-function oxidase system. These metabolites are excreted in the urine; other minor metabolites (carbon dioxide [CO_2] and acetylene) are excreted in expired air. (The acetylene

is formed by reductive dechlorination of 1,1,1-trichloroethane under conditions of low oxygen supply.) Experiments with animals and humans have demonstrated that only small fractions of absorbed 1,1,1-trichloroethane doses (<10%) are metabolized, regardless of the route of exposure. The toxicokinetic behavior of 1,1,1-trichloroethane has the same qualitative pattern in humans, rats, and mice; however, some quantitative differences among these species have been observed, including a higher blood:air partition coefficient and an increased rate of metabolism in mice compared with rats and humans. Physiologically-based pharmacokinetic models have been developed to describe the kinetic behavior of 1,1,1-trichloroethane in mice, rats, and humans; these models have been used to make interspecies and interroute extrapolations in estimating 1,1,1-trichloroethane exposure levels in humans that will produce (or not produce) toxic effects (Bogen and Hall 1989; Dallas et al. 1989; Leung 1992; Nolan et al. 1984; Reitz et al. 1988; USAF 1990).

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

Data from experiments in which humans were exposed for short periods to 1,1,1-trichloroethane vapors indicate that the compound is rapidly and extensively absorbed by the respiratory system. 1,1,1-Trichloroethane was detected in the arterial blood of men within . 10 seconds after exposure to 250 or 350 ppm (Astrand et al. 1973). When subjects held single breaths of air containing radiolabeled 1,1,1-trichloroethane for 15–40 seconds, alveolar concentrations decreased to between 10 and 20% of the initial concentrations, indicating extensive absorption upon initial exposure (Morgan et al. 1972a, 1972b). The extent of absorption of inhaled 1,1,1-trichloroethane decreases with continued exposure to the compound, as concentrations in alveolar air, blood, and tissues attain near equilibrium or steady state. Average lung retentions of 25–30% were measured in humans exposed to 35–350 ppm for 4–6 hours (i.e., the concentration of 1,1,1-trichloroethane in expired air after 4–6 hours of exposure equaled 70–75% of the inspired concentration) (Monster et al. 1979; Nolan et al. 1984). Physical exercise during 0.5–4-hour exposures increased systemic absorption of 1,1,1-trichloroethane, due to increased alveolar ventilation and cardiac output (Astrand et al. 1973; Monster et al. 1979). While steady-state levels in blood are approached within the first hours after exposure begins (Astrand et al. 1973; Monster et al. 1979; Nolan et al. 1984), Nolan et al. (1984) predicted, using a physiologically-based kinetic model, that 12 consecutive 6-hour daily exposures (presumably to concentrations of 350 ppm) would be required for 1,1,1-trichloroethane in body tissues to reach 95% of steady state. Absorption is expected to be relatively low after

steady state is reached, because the initial extensive absorption of 1,1,1-trichloroethane is the result of blood and tissue loading (which in turn are affected by respective blood:air and tissue:blood partition coefficients), tissue volumes and blood flows, and low metabolism. Blood:air partition coefficients for humans, rats, and mice were 2.53, 5.76, and 10.8, respectively (Reitz et al. 1988), meaning that small rodents will experience greater systemic uptake than humans, with mice receiving the highest dose. Mice also have the highest respiratory and circulatory rates, two additional factors that significantly influence systemic absorption of 1,1,1-trichloroethane. 1,1,1-Trichloroethane is poorly metabolized in humans and animals (see Section 3.4.3).

Animal experiments provide supporting evidence that inhaled 1,1,1-trichloroethane is rapidly and extensively absorbed and that the absorption, during short-term exposures, is influenced by ventilation rate. In rats exposed to 50 or 500 ppm, percentage uptake decreased from . 80% at the onset of exposure to . 50% after 2 hours of exposure to 50 or 500 ppm. 1,1,1-Trichloroethane was detected in arterial blood within 2 minutes of the onset of exposure and approached steady-state concentrations within 2 hours (Dallas et al. 1989). In anesthetized dogs under regulated respiration conditions, 1,1,1-trichloroethane was detected in arterial blood within 2 minutes of the onset of exposure to 700, 1,500, or 3,000 ppm. Arterial blood concentrations approached steady-state levels within 1 hour at 700 ppm, but not at 1,500 or 3,000 ppm; absorption increased with increases in pulmonary ventilation rate (Hobara et al. 1982, 1983a, 1983b).

3.4.1.2 Oral Exposure

Data regarding the rate or extent of absorption of ingested 1,1,1-trichloroethane in humans are not available, but based on extensive animal data, it is anticipated that oral absorption of 1,1,1-trichloroethane will be extensive in humans. Animal experiments indicate that 1,1,1-trichloroethane is rapidly and completely absorbed by the gastrointestinal tract. Maximum levels of 1,1,1-trichloroethane in venous blood of rats were detected within 10–15 minutes of gavage administration of a 14.2 mg/kg dose in water (Reitz et al. 1988). In experiments in which rats were given an 8-hour free access to drinking water containing [2-^{14}C]-labeled 1,1,1-trichloroethane, radioactivity in expired air, urine, and selected tissues (assayed 56 hours following cessation of access to the labeled water) represented 95.2% of the average dose of 116 mg/kg, indicating nearly complete absorption of the administered dose (Reitz et al. 1988). In experiments with rats and mice given single gavage doses of radiolabeled 1,1,1-trichloroethane in vegetable oil ranging from 100 to 3,000 mg/kg, dose-recovery in expired air ranged from 90 to 97% (RTI

1987). Nearly complete absorption of orally administered 1,1,1-trichloroethane was also indicated in experiments in which rats or mice were pretreated with daily doses of the compound in corn oil for 4 weeks (3,000 and 1,000 mg/kg/day for rats and mice, respectively) before radiolabeled compound was administered to measure absorption and elimination. Radioactivity in expired air and urine (collected for 48 hours after administration) accounted for 88–98% of the administered doses (Mitoma et al. 1985).

Absorption from the gastrointestinal tract is more rapid for 1,1,1-trichloroethane given in water than in vegetable oils, because the oils act as a reservoir for the chemical in the gut, so that most of the chemical remains in the oil in the gut until the oil is digested and absorbed.

3.4.1.3 Dermal Exposure

1,1,1-Trichloroethane is absorbed through human skin. The compound was detected in alveolar air of volunteers during 30-minute skin absorption experiments (Stewart and Dodd 1964). The skin was exposed to the undiluted compound by thumb or hand immersion or topical application to the hand. The amount of 1,1,1-trichloroethane absorbed depended on the surface area of exposed skin and the method of exposure (i.e., immersion or topical application). 1,1,1-Trichloroethane concentrations in blood and alveolar air were 3–4 µg/mL and 2–5 ppm, respectively, immediately following the last of three daily, 2-hour exposures of 12.5 cm^2 areas of covered forearm skin in experiments with other subjects (Fukabori et al. 1977). A dermal absorption rate of 56 nmol 1,1,1-trichloroethane/minute/cm^2 was calculated for human subjects exposed for 3 minutes to liquid 1,1,1-trichloroethane (neat) on a 3-cm^2 area of forearm skin (Kezic et al. 2001). A maximum absorption rate of 0.005 nmol/hour into the blood was reported for volunteers whose forearm and hand (approximately 1,000 cm^2 of surface area) were exposed to 1,1,1-trichloroethane vapors (concentration of about 38,000 ppm) for 20 minutes (Kezic et al. 2000). Dermal absorption rates were 45.7 nmol/minute/cm^2 in mice after 2.92-cm^2 areas of skin were exposed to undiluted compound for 15 minutes under occluded conditions to prevent evaporative loss (Tsuruta 1975). In rats, . 30% of a 2 mL volume of undiluted 1,1,1-trichloroethane was absorbed by a 3.1-cm^2 area of skin in 24 hours under occluded conditions (Morgan et al. 1991). It should be noted that under occluded conditions, which prevent evaporation, concentrated 1,1,1-trichloroethane will defat the skin and promote its own systemic absorption by disrupting the stratum corneum, the actual barrier to penetration. These are not conditions likely to occur in exposed people, however. There is no information available on the extent and rapidity of percutaneous absorption of 1,1,1-trichloroethane from aqueous solutions, a far more likely source of dermal contact, albeit at much lower dose rates.

1,1,1-Trichloroethane vapors will be absorbed through exposed skin to some extent, although absorption through the respiratory tract will predominate during whole-body exposure. Quantitative examination of the relative magnitudes of percutaneous and respiratory absorption in humans equipped with respiratory protection showed that a whole-body exposure to 600 ppm 1,1,1-trichloroethane for 3.5 hours would deliver a dermal dose equivalent to an absorbed inhalation dose from exposure to only . 0.6 ppm over the same period (Riihimaki and Pfaffli 1978).

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

No studies were located regarding the distribution of 1,1,1-trichloroethane to human tissues after inhalation exposure. Nevertheless, 30 autopsies revealed detectable levels of the compound in subcutaneous and renal fat, liver, lung, and muscle (Alles et al. 1988).

Animal studies indicate that inhaled 1,1,1-trichloroethane is distributed by the blood to tissues and organs throughout the body, with preferential distribution to fatty tissues. 1,1,1-Trichloroethane is rapidly cleared from tissues after exposure ceases (Holmberg et al. 1977; Schumann et al. 1982a; Takahara 1986b). Concentrations of 1,1,1-trichloroethane were higher in the liver than in the blood, kidneys, and brain of mice exposed to 10–10,000 ppm for 0.5–24 hours (fatty tissues were not analyzed separately) (Holmberg et al. 1977). In mice exposed to 1,000 ppm for 1 hour, tissue concentrations immediately after exposure displayed the following order: fat > liver > kidney > spleen = blood > lung = heart = brain (Takahara 1986b). In mice and rats exposed to 150 or 1,500 ppm 1,1,1-trichloroethane for 6 hours, concentrations were much (. 11–26-fold) higher in fatty tissue than concentrations in the liver and kidneys immediately following exposure (Schumann et al. 1982a). In male dogs that were exposed to 10,000 ppm of 1,1,1-trichloroethane for 3 minutes (4 times at 4-hour intervals), wet weight concentrations of 1,1,1-trichloroethane, 4 hours after the last exposure, showed the following order: abdominal fat > renal fat > brain ≈ liver ≈ kidney ≈ lungs (Katagiri et al. 1997). Experiments in which pregnant mice were exposed by inhalation to 1,1,1-trichloroethane showed that the compound also is distributed to fetuses (Shimada 1988; Danielsson et al. 1986). Following a 1-hour exposure of pregnant mice to 1,000 ppm, concentrations of 1,1,1-trichloroethane in maternal organs, fetuses, and placentas ranked in the following order: fat > blood > kidney > liver > placenta > brain > fetus (Shimada 1988).

3.4.2.2 Oral Exposure

No studies were located regarding the distribution of 1,1,1-trichloroethane to human tissue after oral exposure to the compound. Ingested 1,1,1-trichloroethane, however, is probably widely distributed among tissues, with preferential accumulation in fatty tissues, based on results of animal studies. Distribution of 1,1,1-trichloroethane to tissues will be governed by several factors, including tissue blood flow rate, tissue volume, and tissue:blood partition coefficient, the latter factor being probably the most important. Following gavage administration of 1,1,1-trichloroethane in vegetable oil to rats (100, 300, or 1,000 mg/kg) or mice (300, 1,000, or 3,000 mg/kg), the compound was distributed to tissues throughout the body, with preferential accumulation in fatty tissues (RTI 1987).

3.4.2.3 Dermal Exposure

No studies were located regarding the distribution of 1,1,1-trichloroethane among human or animal tissues following dermal exposure; however, dermally applied 1,1,1-trichloroethane, once absorbed, is probably widely distributed among tissues, with preferential accumulation in fatty tissues, based on results from oral and inhalation studies with animals.

3.4.2.4 Other Routes of Exposure

Measurements of the tissue distribution of ^{14}C-1,1,1-trichloroethane or its metabolites in rats or mice 24 hours after an intravenous injection indicate a distribution pattern similar to that after oral or inhalation exposure; adipose tissue contained higher concentrations than skeletal muscle, liver, or skin tissue (RTI 1987).

3.4.3 Metabolism

Metabolism appears to play a relatively minor role in the overall disposition of 1,1,1-trichloroethane in humans and animals. Only a small fraction of the absorbed dose (<10%) is metabolized; a large fraction of the absorbed dose is excreted unchanged in exhaled air, regardless of the exposure route. In humans exposed to 70 or 145 ppm 1,1,1-trichloroethane in air for 4 hours, an estimated 60–80% of the absorbed

compound was excreted unchanged in exhaled breath (Monster et al. 1979). Metabolites in urine, trichloroethanol and trichloroacetic acid, collected for 70 hours postexposure represented approximately 2 and 0.5%, respectively, of the 1,1,1-trichloroethane initially absorbed. In humans exposed to 35 or 350 ppm for 6 hours, >91% of absorbed 1,1,1-trichloroethane was excreted unchanged by the lungs, 5–6% was metabolized and excreted as trichloroethanol and trichloroacetic acid, and <1% remained in the body after 9 days (Nolan et al. 1984).

In rats and mice dosed by gavage with 1,1,1-trichloroethane in vegetable oil 5 days/week for 4 weeks, followed by a single dose of ^{14}C-labeled compound, 85.1 and 92.3% of the doses (3,000 and 4,000 mg/kg in rats and mice, respectively) were recovered as unchanged compound in expired air; respective recovery percentages of metabolite fractions (48 hours after administration) in rats and mice were 0.9 and 2.0% as CO_2, 2.1 and 3.4% as metabolites in urine, and 1.2 and 0.7% as presumed metabolites remaining in the carcasses (Mitoma et al. 1985). Similarly, exhalation of unchanged compound was the predominant pathway for elimination of absorbed 1,1,1-trichloroethane, accounting for >90% of doses administered in drinking water studies with rats (Reitz et al. 1988) and in inhalation studies with rats and mice (Schumann et al. 1982a). Comparison of metabolic disposition in mice and rats indicated that mice metabolized 2–3 times more 1,1,1-trichloroethane on a body weight basis; however, in both species, metabolism was a dose-dependent, saturable process that represented a minor route of elimination (Schumann et al. 1982a, 1982b).

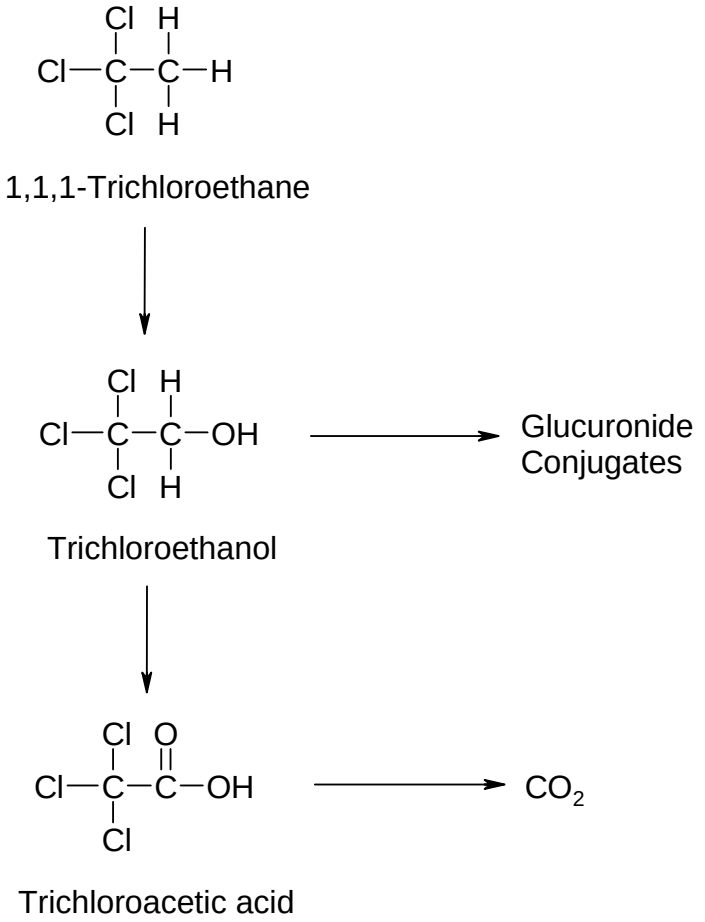
Analysis of urine following human and animal exposure to 1,1,1-trichloroethane identified trichloroethanol, trichloroethanol glucuronide, and trichloroacetic acid as major metabolites of 1,1,1-trichloroethane; CO_2, identified in exhaled breath, is the other major metabolite (Kawai et al. 1991; Mitoma et al. 1985; Monster et al. 1979; Nolan et al. 1984; Reitz et al. 1988; Schumann et al. 1982a). Figure 3-3 illustrates a general metabolic scheme for 1,1,1-trichloroethane. The initial oxidation step is thought to be catalyzed by the microsomal cytochrome P-450 mixed-function oxidase system. In vitro reaction mixtures containing rat hepatic microsomes and nicotinamide adenine dinucleotide phosphate (reduced form) (NADPH) oxidize 1,1,1-trichloroethane to trichloroethanol. 1,1,1-Trichloroethane metabolism significantly increased when microsomes from rats pretreated with phenobarbital, an inducer of certain isozymes of cytochrome P-450, were used. This finding provides supporting evidence of the involvement of this enzyme system in the metabolism, albeit limited, of 1,1,1-trichloroethane (Ivanetich and Van den Honert 1981; Koizumi et al. 1983). The pathway for conversion of trichloroethanol to trichloroacetic acid presumably involves the intermediate formation of chloral hydrate and may involve alcohol and aldehyde

dehydrogenases or cytochrome P-450 mixed-function oxidases (Casciola and Ivanetich 1984; Ivanetich and Van den Honert 1981). Although trichloroacetic acid or chloral hydrate were not detected as in vitro metabolic products of 1,1,1-trichloroethane with rat hepatic microsomal cytochrome P-450 preparations (Ivanetich and Van den Honert 1981; Koizumi et al. 1983), in vitro production of chloral hydrate from 1,1,1-trichloroethane was demonstrated in reaction mixtures containing rat nuclei cytochrome P-450 preparations (Casciola and Ivanetich 1984).

In vivo and *in vitro* evidence from rat experiments suggests that, under conditions of low oxygen supply, 1,1,1-trichloroethane can be reductively dechlorinated, to a limited extent, to radical intermediates and eventually to acetylene (Durk et al. 1992); in these experiments, exhaled acetylene accounted for <1% of metabolized 1,1,1-trichloroethane. The reductive dechlorination of 1,1,1-trichloroethane appears to be mediated by cytochrome P-450, since putative induction by phenobarbital treatment accelerated the in vitro and in vivo metabolic formation of acetylene. The reductive metabolic pathway is not indicated in Figure 3-3, because it apparently represents a very minor metabolic pathway.

Repeated exposure of mice and rats to 1,1,1-trichloroethane apparently does not increase the relative importance of metabolism to the *in vivo* disposition of the compound (Schumann et al. 1982b), even though another research group reported that hepatic microsomes from rats exposed continuously for 10 days to 800 ppm of 1,1,1-trichloroethane displayed greater in vitro enzymatic activities for 1,1,1-trichloroethane oxidation than microsomes from fresh-air controls (Koizumi et al. 1983). Schumann et al. (1982b) found that repeated exposure of rats or mice to 1,500 ppm unlabeled 1,1,1-trichloroethane for 16 months did not alter the routes of excretion, the extent of metabolism, or the concentration of radioactivity in tissues after a 6-hour inhalation exposure to 1,500 ppm [2–^{14}C]-1,1,1-trichloroethane, compared with age-matched animals subjected to single 6-hour exposures. In general, studies regarding the effects of 1,1,1-trichloroethane on hepatic enzyme induction are inconclusive. Although Koizumi et al. (1983) and others (Bruckner et al. 2001; Fuller et al. 1970; Lal and Shah 1970) reported that 1,1,1-trichloroethane induced hepatic cytochrome P-450 enzyme levels in rats, others observed no effects (Toftgaard et al. 1981; Wang et al. 1996) or inhibitory effects (Nakahama et al. 2000; Savolainen et al. 1977) in rats exposed to 1,1,1-trichloroethane.

Figure 3-3. Metabolic Scheme for 1,1,1-Trichloroethane



3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

After acute exposure, most inhaled 1,1,1-trichloroethane is rapidly excreted unchanged in expired air of humans and animals. Within 1 hour of administration, humans exhaled 44% of the radioactivity they had inhaled from a single breath of radiolabeled 1,1,1-trichloroethane (Morgan et al. 1970). Humans exposed to 70 or 145 ppm for 4 hours exhaled 60–80% of inhaled 1,1,1-trichloroethane unchanged during a 150-hour period after exposure (Monster et al. 1979). Other humans exposed to 35 or 350 ppm for 6 hours exhaled >91% of absorbed 1,1,1-trichloroethane as the unchanged compound within 9 days of exposure (Nolan et al. 1984). Similar observations were made in studies of rats (Ikeda and Ohtsuji 1972; Schumann et al. 1982a, 1982b), mice (Schumann et al. 1982a, 1982b), and anesthetized dogs (Hobara et al. 1982). Nolan et al. (1984) described the temporal elimination pattern for 1,1,1-trichloroethane in blood and expired air of humans as "triexponential" and estimated half-lives of 44 minutes, 5.7 hours, and 53 hours for the initial, intermediate, and terminal phases, respectively. Raymer et al. (1991) used a two-compartment model to fit experimental observations of the temporal decrease in 1,1,1-trichloroethane concentrations in human breath samples collected for 4 hours after exposure to contaminated atmospheres; elimination half-lives ranged from 0.00 to 0.17 hours for the first compartment and from 1.80 to 6.08 hours for the second compartment.

Exhalation of CO_2 and urinary excretion of metabolites (trichloroethanol and trichloroacetic acid) represent minor elimination pathways for inhaled 1,1,1-trichloroethane. Nevertheless, observed correlations between urinary concentrations of 1,1,1-trichloroethane metabolites and exposure concentrations indicate that urine analysis may be a useful method of exposure assessment (Caperos et al. 1982; Ghittori et al. 1987; Imbriani et al. 1988; Kawai et al. 1991; Mizunuma et al. 1995; Seki et al. 1975). Estimated half-lives for the elimination of trichloroethanol and trichloroacetic acid from human blood after inhalation exposures to 1,1,1-trichloroethane were 10–27 hours for trichloroethanol and 70–85 hours for trichloroacetic acid (Monster et al. 1979; Nolan et al. 1984). The long half-life of trichloroacetic acid is due to binding of this metabolite to plasma proteins. Daily occupational exposure to 1,1,1-trichloroethane progressively increased urinary metabolite levels during the workweek, while levels decreased over the weekend (Seki et al. 1975). This observation is consistent with observations of the rapid clearance of 1,1,1-trichloroethane and its metabolites from animal tissues after inhalation exposure (Dallas et al. 1989; Holmberg et al. 1977; Schumann et al. 1982a, 1982b; Takahara 1986a).

3.4.4.2 Oral Exposure

Humans eliminate ingested 1,1,1-trichloroethane in their exhaled breath (Stewart and Andrews 1966), but no studies were located that quantified excretion rates or the extent of excretion. The pattern of elimination is expected to be similar to that of inhaled 1,1,1-trichloroethane (i.e., exhalation of unchanged 1,1,1-trichloroethane should be the predominant route of excretion; exhalation of CO_2 and urinary excretion of other metabolites are minor routes). This pattern has been observed in animals after inhalation (see Section 3.4.4.1) and oral exposure (Mitoma et al. 1985; Reitz et al. 1988; RTI 1987). In rats exposed to 1,1,1-trichloroethane in drinking water for 8 hours (total dose of 116 mg/kg), the primary route of excretion was rapid elimination of unchanged 1,1,1-trichloroethane in expired air; only 3% of the ingested dose was metabolized (Reitz et al. 1988). Essentially all of the ingested 1,1,1-trichloroethane was excreted within 30 hours. Similar results were obtained in gavage studies with rats and mice (Mitoma et al. 1985; RTI 1987). Excretion via the mother's milk does not appear to be a significant route of excretion for 1,1,1-trichloroethane. Approximately 0.04% of an orally-administered dose of 1,1,1-trichloroethane was excreted in the 24-hour milk of lactating goats (Hamada and Tanaka 1995).

3.4.4.3 Dermal Exposure

The pattern of excretion in humans after dermal exposure is expected to be similar to that of inhaled 1,1,1-trichloroethane: rapid exhalation of 1,1,1-trichloroethane in expired air is the major excretion route; exhalation of CO_2 and urinary excretion of other metabolites are minor routes (see Section 3.4.4.1). Several studies have measured 1,1,1-trichloroethane in the expired breath of humans after (and during) short-term dermal exposure to 1,1,1-trichloroethane (Fukabori et al. 1977; Riihimaki and Pfaffli 1978; Stewart and Dodd 1964), but 1,1,1-trichloroethane exhalation as a percentage of absorbed dose was not quantitated in these studies.

Results in animals given 1,1,1-trichloroethane injections indicate that excretion patterns in animals are similar regardless of route. In mice given intraperitoneal injections of 1,1,1-trichloroethane, 88% of the dose was excreted unchanged in expired air and 1% was excreted as metabolites in urine (Takahara 1986b). In rats given intraperitoneal injections, 98.7% of the dose was exhaled as unchanged 1,1,1-trichloroethane (Hake et al. 1960). Within 24 hours of intravenous injection of radiolabeled 1,1,1-trichloroethane, exhalation of radioactivity accounted for 91 and 80% of the administered doses in rats and mice,

respectively; only trace amounts of radioactivity remained in the tissues after 24 hours (RTI 1987). In dogs, 60–70% of intravenously injected 1,1,1-trichloroethane was excreted in expired air within 1 hour (Hobara et al. 1981).

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 et al. 1987; Andersen and Krishnan 1994). 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 parametrization, (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.

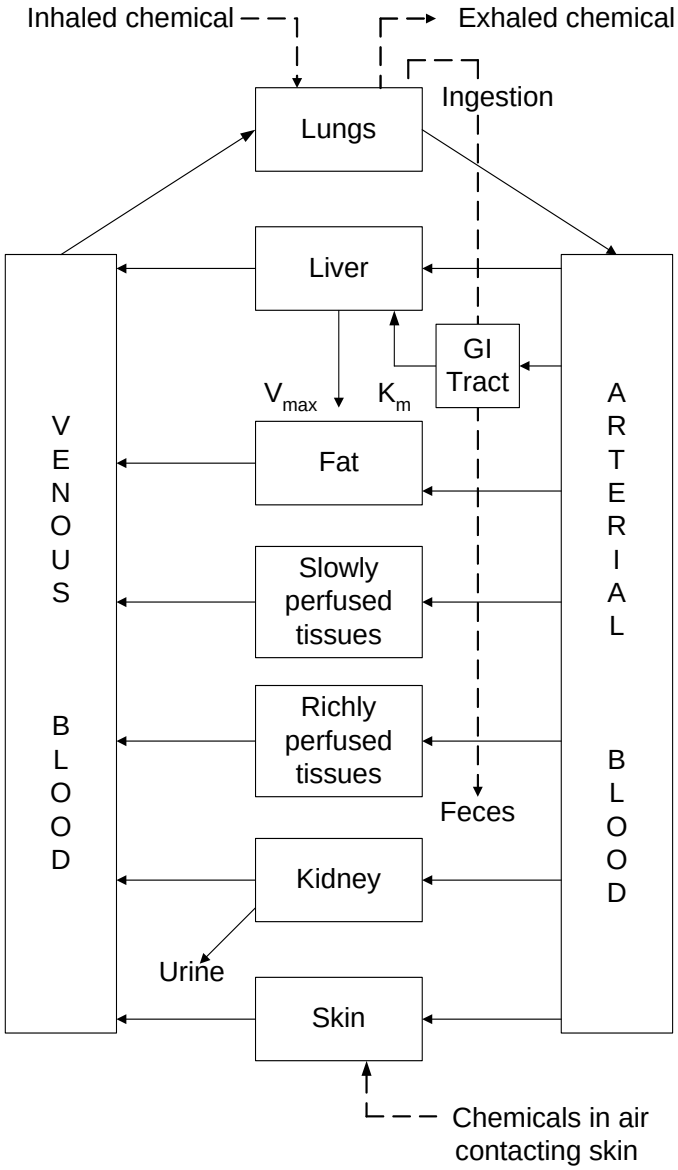
PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in 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.

Literature search revealed a PBPK model for 1,1,1-trichloroethane in rats, mice, and humans (Reitz et al. 1988) that was based on a four-compartment model developed for styrene (Ramsey and Andersen 1984). Adaptations of the Reitz et al. (1988) model were presented by others (Bogen and Hall 1989; Dobrev et al. 2001, 2002; Poet et al. 2000).

Reitz et al. (1988) 1,1,1-Trichloroethane Biokinetics Model

Description of the Model. Reitz et al. (1998) developed a four-compartment model for rats, mice, and humans, which predicts the behavior of inhaled 1,1,1-trichloroethane in liver, rapidly perfused tissue, slowly perfused tissue, and fat. Tissue volumes and blood and airflow rates employed in the model are listed in Table 3-6. The percentage of cardiac output directed to the fat compartments was adjusted for interspecies differences in fat content. Tissue:blood partition coefficients (Table 3-6) were used to calculate the 1,1,1-trichloroethane concentration in venous blood leaving the tissue and were estimated with rat blood, liver, fat, and muscle tissue using a vial-equilibration technique. Blood:air partition

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



Source: adapted from Krishnan et al. 1994

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.

Table 3-6. Parameters Used in the Physiologically Based Pharmacokinetic Model for 1,1,1-Trichloroethane Developed by Reitz et al. (1988)

	Human	Rat	Mouse
Weights			
Body weight (kg)	83.0	0.215	0.029
Liver (%)	3.1	4.0	4.0
Rapidly perfused (%)	3.7	5.0	5.0
Slowly perfused (%)	61.1	75.0	78.0
Fat (%)	23.1	7.0	4.0
Flows (L/hour)			
Alveolar ventilation	348.0	5.11	1.26
Cardiac output (COP)	348.0	5.11	1.26
Liver (% COP)	24.0	24.0	24.0
Rapidly perfused (% COP)	49.0	53.0	56.0
Slowly perfused (% COP)	18.0	18.0	18.0
Fat (% COP)	9.0	5.0	2.0
Partition coefficients			
Blood/air	2.53	5.76	10.8
Liver/air	8.6	8.6	8.6
Rapidly perfused/air	8.6	8.6	8.6
Slowly perfused/air	3.15	3.15	3.15
Fat/air	263	263	263
Biochemical constants[a]			
VmaxC	0.419	0.419	0.419
Km (mg/L)	5.75	5.75	5.75
Ka ($hour^{-1}$) (1^{st}-order rate constant for GI absorption	—	1.25	—

[a]VmaxC and Km were obtained for the rat from the blood level data of Schumann et al. (1982a) by computer optimization. VmaxC is an allometric measure of maximum velocity of metabolism showing the following relationship with maximum enzyme rate: $Vmax = VmaxC \times (body\ weight)^{0.7}$.

COP = cardiac output

coefficients were determined with human and mouse blood. Metabolism was restricted to the liver and was described by Michaelis-Menten kinetics. Metabolic kinetic constants (Vmax and Km; Table 3-6) were estimated by optimization of the model with 1,1,1-trichloroethane blood concentration data for rats exposed by inhalation to 150 or 1,500 ppm for 6 hours (Schumann et al. 1982a). The model was designed to be applicable to exposures via drinking water, bolus gavage, and intravenous administration as well. For drinking water exposures, uptake of 1,1,1-trichloroethane from the gastrointestinal tract and transfer to the liver was assumed to follow zero-order kinetics. Simulation of gavage administration assumed first-order absorption from the gastrointestinal tract, with a rate constant of 1.25/hour. Both oral (drinking water or gavage) and intravenous administration assumed direct transfer to the liver.

Validation of the Model. Predictions based on the model were compared to observed values for experimentally-determined end exposure 1,1,1-trichloroethane blood levels, amount of 1,1,1-trichloroethane metabolized, and concentrations of 1,1,1-trichloroethane in fat or liver of rats and mice following exposure via drinking water or inhalation, and on observed values of the amount of 1,1,1-trichloroethane metabolized in human volunteers following inhalation exposure. Model predictions agreed reasonably well with the empirical observations (Reitz et al. 1988).

Bogen and Hall (1989) adapted the Reitz et al. (1988) rat model to gerbils using a scaling factor and presented a five-compartment model (liver, richly perfused tissues, poorly perfused tissues, fat, and skin) for a 70-kg adult male subject using reference values from EPA (1988m) for tissue-specific volumes, blood perfusion rates, and cardiac output. Values for skin were assumed to be 6% of reference values for poorly perfused tissues. Poet et al. (2000) modified the PBPK model of Reitz et al. (1988) to include a separate skin compartment. Dobrev et al. (2001, 2002) presented a model for mixed exposures to trichloroethylene, tetrachloroethylene, and 1,1,1-trichloroethane.

Fisher et al. (1997) modeled the excretion of 1,1,1-trichlorethane (and other volatile organic chemicals) via the breast milk. Model simulations predicted a low degree (<1%) of lactational transfer of 1,1,1-trichloroethane. However, model predictions were not validated with empirical data.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

1,1,1-Trichloroethane is rapidly and extensively absorbed from the lungs (Astrand et al. 1973; Dallas et al. 1989; Hobara et al. 1982, 1983a, 1983b; Monster et al. 1979; Morgan et al. 1972a, 1972b; Nolan et al. 1984), skin (Fukabori et al. 1977; Morgan et al. 1991; Riihimaki and Pfaffli 1978; Stewart and Dodd 1964; Tsuruta 1975) and gastrointestinal tract (Mitoma et al. 1985; Reitz et al. 1988; RTI 1987; Stewart and Andrews 1966). The lipophilic nature of 1,1,1-trichloroethane, the rates of absorption upon various routes of exposure, and the rates at which the chemical leaves the body in expired air when exposure is terminated all suggest that 1,1,1-trichloroethane is very likely transported across cellular membranes by passive diffusion. No known specific intermediary molecules influence the distribution of 1,1,1-trichloroethane among tissues in the body. The lipophilicity and volatility of 1,1,1-trichloroethane, along with the low rates at which it is metabolized, appear to be the most important factors influencing distribution within and elimination from the body. The compound is widely distributed by the blood among tissues, with preferential accumulation in fatty tissues, and is rapidly cleared following exposure cessation (Holmberg et al. 1977; RTI 1987; Schumann et al. 1982a, 1982b; Takahara 1986b).

As presented in detail in Section 3.4.3, only a small percentage of 1,1,1-trichloroethane absorbed across the lung is metabolized; most of the absorbed dose is excreted unchanged from the lung. For example, a 6-hour exposure to 35 or 350 ppm of 1,1,1-trichloroethane resulted in the metabolism of approximately 5–6% of the absorbed dose, which was excreted in the urine as trichloroethanol or trichloroacetic acid (Nolan et al. 1984). More than 90% was excreted unchanged from the lungs and <1% remained in the body after 9 days. Analysis of urine following human and animal exposure to 1,1,1-trichloroethane identified trichloroethanol, trichloroethanol glucuronide, and trichloroacetic acid as major metabolites of 1,1,1-trichloroethane; CO_2, identified in exhaled breath, is another metabolite (Kawai et al. 1991; Mitoma et al. 1985; Monster et al. 1979; Nolan et al. 1984; Reitz et al. 1988; Schumann et al. 1982a). Figure 3-3 illustrates a general metabolic scheme for 1,1,1-trichloroethane. The initial oxidation step is thought to be catalyzed by the microsomal cytochrome P-450 mixed-function oxidase system. The pathway for conversion of trichloroethanol to trichloroacetic acid presumably involves the intermediate formation of chloral hydrate and may involve alcohol and aldehyde dehydrogenases or cytochrome P-450 mixed-function oxidases (Casciola and Ivanetich 1984; Ivanetich and Van den Honert 1981). The pattern of elimination following oral or dermal exposure is expected to be similar to that of inhaled 1,1,1-trichloro-

ethane (i.e., exhalation of unchanged 1,1,1-trichloroethane should be the predominant route of excretion; exhalation of CO_2 and urinary excretion of other metabolites are minor routes).

3.5.2 Mechanisms of Toxicity

The mechanism by which high levels of 1,1,1-trichloroethane produces mild to moderate hepatotoxic effects in humans and animals is only partially understood. Studies of more potent hepatotoxic chlorinated alkanes (including carbon tetrachloride, chloroform, and 1,1,2-trichloroethane) have clearly demonstrated an involvement of cytochrome P-450-mediated dechlorination in the production of liver injury (Plaa 1986). It has been hypothesized that the production of free radicals via the homolytic cleavage of the carbon-chlorine bond in these hepatotoxic chlorinated alkanes occurs in the endoplasmic reticulum of hepatocytes, and that the free radicals react with unsaturated lipids and proteins in the endoplasmic reticulum, producing lipid peroxidation and covalent binding. These actions lead to morphological and functional changes in this organelle and, eventually, to cellular dysfunction (triglyceride accumulation) and necrosis (Plaa 1986). The potency of the 1,1,2- isomer of trichloroethane to produce liver injury is markedly greater than that of the 1,1,1- isomer (Carlson 1973; Takahara 1986c). This difference has been associated with differences in the metabolic activation of the two isomers. 1,1,2-Trichloroethane is metabolized to a much greater extent than 1,1,1-trichloroethane in mice and rats after gavage administration. Urinary excretion of metabolites accounted for >70% of the administered doses of the 1,1,2- isomer; in contrast, >85% of the administered 1,1,1- isomer dose was excreted unchanged in expired air (Mitoma et al. 1985). In experiments with rat liver microsomes, Van Dyke and Wineman (1971) observed that 9.8% of the chloride was enzymatically removed from the 1,1,2- isomer, compared with <0.5% removal of chloride from the 1,1,1- isomer in the same period. The difference in extent of metabolism of the 1,1,2- and 1,1,1- isomers explains the difference in hepatotoxicity of the two compounds (i.e., the 1,1,2- isomer is more potent because greater quantities of reactive metabolites are produced from it); however, whether the mild hepatotoxicity of 1,1,1-trichloroethane is mediated by a metabolite or by the compound itself is unclear. Carlson (1973) reported that rats pretreated with phenobarbital displayed signs of liver injury (increased levels of SGPT and SGOT and decreased activity of glucose-6-phosphatase) immediately following a 2-hour exposure to 11,600 ppm 1,1,1-trichloroethane; these signs were not apparent in nonpretreated rats exposed to the same 1,1,1-trichloroethane concentration or in rats that had received only the phenobarbital pretreatment. This suggests that metabolic activation is involved in the expression of 1,1,1-trichloroethane's hepatotoxicity. Phenobarbital pretreatment did not potentiate the hepatotoxicity of 1,1,1-trichloroethane in rats following intraperitoneal

injection of 2 mL 1,1,1-trichloroethane/kg (approximately 2.6 mg/kg) (Cornish et al. 1973), but this apparent contrast to the results of Carlson (1973) may reflect differences in exposure scenarios.

Acute exposures to high 1,1,1-trichloroethane concentrations can cause sudden death in humans due to ventricular fibrillation, myocardial depression, or respiratory arrest. Animal studies show that arrhythmias (that can lead to ventricular fibrillation) can be produced by exogenously administered epinephrine during or immediately after inhalation exposure to 1,1,1-trichloroethane (Carlson 1981; Clark and Tinston 1973; Reinhardt et al. 1973; Trochimowicz et al. 1974). 1,1,1-Trichloroethane is one of the most potent of the volatile organic compounds that induce arrhythmias. The studies indicate that the arrhythmias are not caused directly by 1,1,1-trichloroethane, but result from its sensitization of the heart to epinephrine. The basis for the sensitization is not completely understood, but evidence suggests that the sensitization is produced by 1,1,1-trichloroethane itself and not by its metabolites. Carlson (1981) reported that pretreatment of rabbits with phenobarbital (thereby increasing 1,1,1-trichloroethane metabolism) did not increase the incidence of epinephrine-induced arrhythmias during 1-hour exposures to 5,600 ppm, and that treatment with cytochrome P-450 inhibitors (SKF-525A and Lilly 18947) (decreasing the metabolism of 1,1,1-trichloroethane) 30 minutes before exposure to 1,1,1-trichloroethane increased the incidence of epinephrine-induced cardiac arrhythmias. The arrhythmogenicity of 1,1,1-trichloroethane and other halogenated hydrocarbons may involve intercellular communication inhibition, presumably through parent-compound modification of gap junctions between cardiac myocytes. Toraason et al. (1992) demonstrated that a series of halogenated hydrocarbons, including 1,1,1-trichloroethane, inhibited the transfer of a fluorescent probe between adjacent cultured cardiac myocytes isolated from neonatal rats (an assay for gap junction communication) and that the inhibition was not affected by pretreating the cells with SKF-525A. Toraason et al. (1992) noted that the ability of the compounds to inhibit intercellular communication paralleled their ability to sensitize the heart to epinephrine-induced arrhythmias.

Acute exposure to high concentrations of 1,1,1-trichloroethane (≈10,000–26,000 ppm) lowered blood pressure in humans and animals within minutes of exposure (Herd et al. 1974; Kobayashi et al. 1988; McLeod et al. 1987; Wright and Strobl 1984). Studies with anesthetized dogs associated the decrease in blood pressure with peripheral vasodilation at the lower end of the effective concentration range and with decreased heart rate and myocardial contractility at higher concentrations (Herd et al. 1974; Kobayashi et al. 1988). Intravenous administration of phenylephrine (an agent that putatively constricts peripheral vasculature) or calcium counteracted the blood pressure-reducing effects of 1,1,1-trichloroethane in

anesthetized dogs (Herd et al. 1974). Herd et al. (1974) hypothesized that 1,1,1-trichloroethane, because of its lipophilic nature, may produce cardiotoxic effects through an interference with membrane-dependent processes such as adenosine triphosphate (ATP) production by cardiac mitochondria and calcium mobilization during myocardial contraction. More recently, Toraason et al. (1990) demonstrated a reversible, concentration-dependent inhibitory effect of 1,1,1-trichloroethane on the contractility (i.e., decreased beating frequency) of cultured rat heart cells. Hoffman et al. (1992, 1994) showed that 1,1,1-trichloroethane inhibits calcium mobilization during excitation-contraction coupling in isolated ventricular myocytes from rat neonates, and hypothesized that myocardial depression following exposure to 1,1,1-trichloroethane results from reduced intracellular calcium concentration during systole.

Respiratory arrest due to central nervous system depression has been proposed as a possible explanation for sudden deaths following acute exposure to high concentrations of 1,1,1-trichloroethane (Adams et al. 1950; Jones and Winter 1983; Torkelson et al. 1958). In general, the actions of 1,1,1-trichloroethane are very similar to other central nervous system depressants. The mechanism by which acute exposures to high concentrations of 1,1,1-trichloroethane depress the central nervous system is thought to involve interactions of the parent compound with lipids and/or proteins in neural membranes that lead to dysfunction (Evans and Balster 1991). In general, the highly lipophilic nature of chlorinated hydrocarbons, such as 1,1,1-trichloroethane, 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 et al. 1996).

1,1,1-Trichloroethane-induced hepatic, neurological, and cardiac effects may be related to the interaction of 1,1,1-trichloroethane with proteinaceous components of membranes, as suggested by demonstrations that 1,1,1-trichloroethane inhibits the activity of membrane-bound enzymes such as acetylcholinesterase and magnesium-activated ATPase in human red blood cells and rat synaptosomes (Korpela 1989; Korpela and Tähti 1986, 1987; Tähti and Korpela 1986). Such an interaction could be responsible for the observed 1,1,1-trichloroethane-induced alterations in membrane permeability that have been demonstrated in brain synaptosomes (Nilsson 1987; Robinson et al. 2001) and dorsal root ganglion neurons (Okuda et al. 2001a, 2001b), cardiac myocytes (Hoffmann et al. 1992, 1994; Toraason et al. 1990), and rat heart and liver mitochondria (Herd and Martin, 1975). Altered calcium permeability has been demonstrated to cause reduced contractility of cardiac myocytes (Hoffmann et al. 1992, 1994; Torasson et al. 1990) and uncoupled oxidative phosphorylation leading to reduced cellular respiration and

ATP production in rat heart and liver mitochondria (Herd and Martin 1975; Ogata and Hasegawa 1981; Takano and Miyazaki 1982).

3.5.3 Animal-to-Human Extrapolations

Species-specific differences in pharmacokinetic properties of inhaled 1,1,1-trichloroethane have been demonstrated. Nolan et al. (1984) reported 2.5- and 3-fold greater absorption in rats and mice, respectively, relative to humans following equivalent inhalation exposures. Measured blood levels in the rats and mice were 3.5- and 17.3-fold higher than humans, and the amount of 1,1,1-trichloroethane metabolized was 4.3-fold higher in rats and 11.4-fold higher in mice than humans. These results indicate that humans would have to be exposed to 1,1,1-trichloroethane vapor concentrations much higher than those of rats and mice in order to achieve similar blood levels. Although pharmacokinetic differences are readily apparent, species-specific differences in pharmacodymanics have not been elucidated.

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 Colborn and Clement (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).

1,1,1-Trichloroethane does not appear to act on the neuroendocrine axis, although the database of information is limited. In an acute-duration study, no histopathological changes were seen in the adrenals of rats after a single 2-hour exposure to up to 15,000 ppm 1,1,1-trichloroethane (Cornish and Adefuin 1966). Plasma corticosterone levels were statistically significantly decreased in rats after inhalation exposure to 1,1,1-trichloroethane at a concentration of 3,500 ppm for 30 minutes or 5,000 ppm for 10 or 30 minutes; the highest exposure level also resulted in significantly reduced plasma adrenocorticotropic hormone (Pise et al. 1998). Additional information regarding the potential for 1,1,1-trichloroethane to act as an endocrine disruptor was not located.

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).

No information was located regarding potential age-related differences in susceptibility to 1,1,1-trichloroethane in humans. Delays in developmental milestones (pinnae detachment, incisor eruption, and eye

opening) and impaired performance in neurobehavior tests were noted in mouse pups of dams exposed to 1,1,1-trichloroethane during later stages of gestation at levels that did not result in apparent maternal toxicity (Jones et al. 1996). These results suggest that developing organisms may be more susceptible than adults to the toxic effects of 1,1,1-trichloroethane.

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 or 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 1,1,1-trichloroethane 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

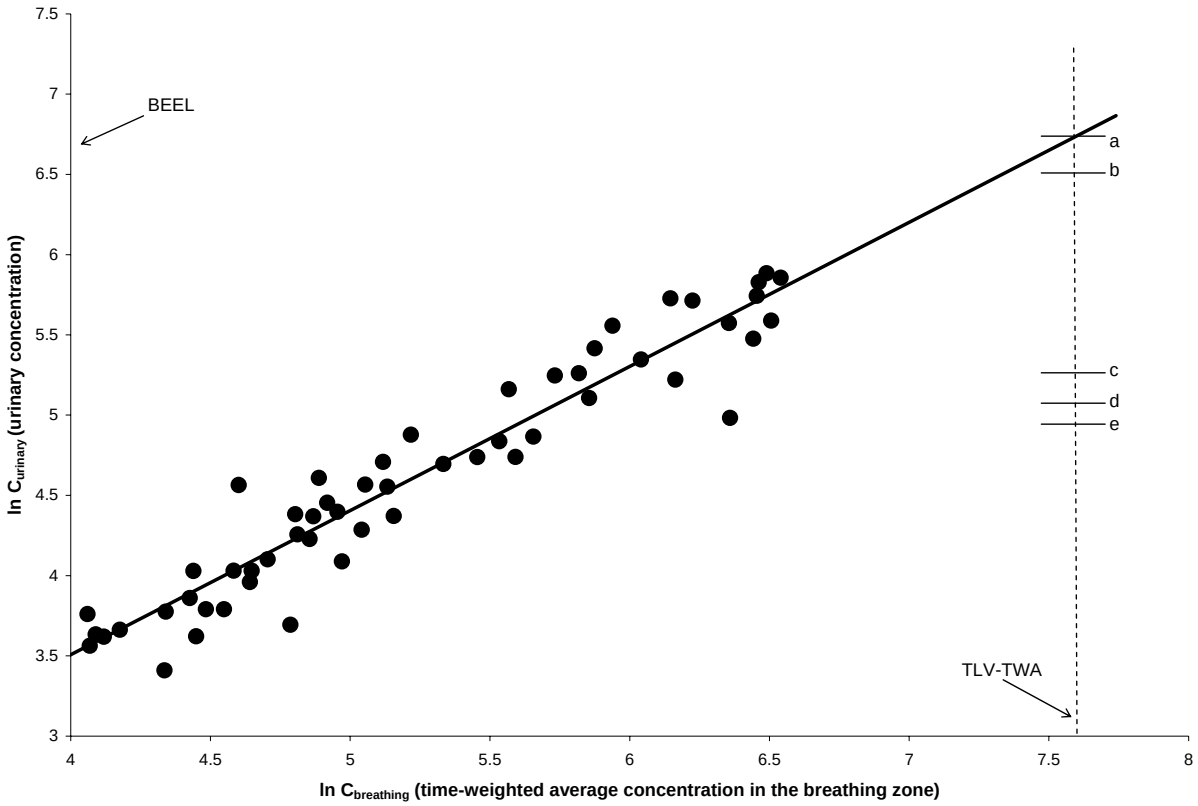
adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by 1,1,1-trichloroethane are discussed in Section 3.8.2.

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 1,1,1-Trichloroethane

Environmental levels of 1,1,1-trichloroethane have been correlated with levels in expired air, blood, and urine. After extensive studies, a significant correlation was observed between the environmental exposure of humans to 1,1,1-trichloroethane and levels of the chemical in expired air in various U.S. locations during various seasons (Hartwell et al. 1987a; Wallace et al. 1982, 1984b, 1985, 1987a, 1987b, 1987c). Levels of 1,1,1-trichloroethane and its metabolites, trichloroethanol and trichloroacetic acid, have been quantified in the blood, expired air, and urine of workers exposed to 50 ppm 1,1,1-trichloroethane for 1 week (Monster 1986). Immediately following exposure, urine levels of trichloroethane and trichloroacetic acid were 4.9 and 2.5 mg/g creatinine, respectively. At 5–15 minutes after exposure, 1,1,1-trichloroethane levels in the blood and expired air were 0.9 mg/L and 210 mg/m^3, respectively. The blood levels of trichloroethanol and trichloroacetic acid were 0.16 and 2.3 mg/L, respectively. For comparison, the baseline level of 1,1,1-trichloroethane in the blood of unexposed, normal subjects was 0.0002 mg/L (range <0.0001–0.0034 mg/L) and the blood level of trichloroacetic acid was 0.0214 mg/L (Hajimiragha et al. 1986). Studies of 1,1,1-trichloroethane levels in expired air or its metabolites in the urine have established a linear correlation between urinary trichloroethanol concentrations and environmental 1,1,1-trichloroethane levels or 1,1,1-trichloroethane levels absorbed through the lungs (Ghittori et al. 1987; Imbriani et al. 1988; Mizunuma et al. 1995; Monster 1986; Pezzagno et al. 1986; Seki et al. 1975; Stewart et al. 1961). Data from Imbriani et al. (1988) are presented in Figure 3-5. Monster (1986) proposed that the best method for estimating occupational exposure to 1,1,1-trichloroethane was to determine the levels of 1,1,1-trichloroethane and trichloroacetic acid in blood after work on Fridays. Results of Mizunuma et al. (1995) indicated that urinary levels of 1,1,1-trichloroethane (as parent compound) were more closely correlated to 1,1,1-trichloroethane in the ambient air of a group of 50 solvent workers than the major urinary metabolites, trichloroethanol and trichloroacetic acid. Among

Figure 3-5. Scatter Diagram Relating Time-Weighted Average of Environmental Concentration and Urinary Concentration of 1,1,1-Trichloroethane in Exposed Workers*



Scatter diagram relating the time-weighted average (TWA) of the environmental concentration (in the breathing zone) ($C_{breathing}$) and the urinary concentration ($C_{urinary}$) of 1,1,1-trichloroethane in the exposed workers (Experiment II). The regression line ($C_{urinary}$=0.45x$C_{breathing}$+12.6; r=0.95; N=60) is also drawn.
a $C_{urinary}$ value at $C_{breathing}$ = 1,900 mg/m^3 (threshold limit value [TLV] -TWA)
b 95% lower confidence limit = biological exposure limit
c hypothetical value of $C_{urinary}$ in an occupationally exposed subject
d one-sided upper confidence limit (at 95%) of $C_{urinary}$
e one-sided lower confidence limit (at 95%) of $C_{urinary}$

Classification system:
1 d<b (or d/b<1) = compliance exposure
2 e>b (or e/b>1) = noncompliance exposure
3 any individual which cannot be classified in 1 or 2 = possible overexposure

The $C_{breathing}$ and $C_{urinary}$ values are shown in 1n numbers to allow all data in a same diagram. The TLV-TWA is 19,900 mg/m^3 (anti-ln 7.549).
The biological equivalent exposure limit (BEEL) is 805 µ/L (anti-ln 6.690).

*Adapted from Imbriani et al. 1988

four adult volunteers (two males and two females) exposed to several different concentrations of 1,1,1-trichloroethane vapors for various exposure durations, levels of parent compound in alveolar air and blood were more closely correlated with exposure level than urinary levels of parent compound or 1,1,1-trichloroethane metabolites (Laparé et al. 1995).

The length of time between 1,1,1-trichloroethane exposure and the measurement of breath, blood, or urine levels is critical to the accurate evaluation of the magnitude of exposure. Up to 90% of the 1,1,1-trichloroethane absorbed by any route is rapidly excreted unchanged in the expired air (Monster et al. 1979; Morgan et al. 1970, 1972b; Nolan et al. 1984; Stewart et al. 1961, 1969). Most of the remaining 10% is accounted for as the urinary metabolites trichloroethanol and trichloroacetic acid. Furthermore, 1,1,1-trichloroethane is rapidly eliminated from the body; ≥99% is eliminated within 50 hours (Astrand et al. 1973; Monster et al. 1979; Nolan et al. 1984; Stewart et al. 1961). See Section 3.4 for more information regarding the pharmacokinetics of 1,1,1-trichloroethane. The appearance of trichloroacetic acid in urine is not unique to 1,1,1-trichloroethane, as it has also been identified as a urinary metabolite of trichloroethylene and tetrachloroethylene (Monster 1988). If exposure is known to be solely to 1,1,1-trichloroethane, trichloroacetic acid levels in the urine may be a useful biomarker of exposure, because of the relatively long half-life of trichloroacetic acid.

3.8.2 Biomarkers Used to Characterize Effects Caused by 1,1,1-Trichloroethane

The central nervous system is apparently the most sensitive tissue to 1,1,1-trichloroethane exposure. Decreased psychomotor performance, altered EEG recordings, ataxia, and anesthesia have been observed in humans after acute exposure (Dornette and Jones 1960; Mackay et al. 1987; Muttray et al. 2000; Sot et al. 1975; Torkelson et al. 1958). Mild hepatic effects and decreased blood pressure have also been noted (Cohen and Frank 1994; Croquet et al. 2003; Dornette and Jones 1960; Stewart et al. 1961; Texter et al. 1979). Numerous animal studies provide supporting evidence for the sensitivity of the central nervous system to acute and intermediate-duration exposure to 1,1,1-trichloroethane. Adverse cardiovascular effects and mild hepatic effects have also been observed in animals. Indices of central nervous system, hepatic, and cardiovascular effects are of limited value as biomarkers, since many other lipophilic chemicals (including some likely to be present at the same sites as 1,1,1-trichloroethane) may cause similar effects in these target organs.

No specific biomarkers of effects caused by 1,1,1-trichloroethane were found in the literature. Additional information regarding the effects of exposure to 1,1,1-trichloroethane can be found in OTA (1990) and ATSDR (1990). For a more detailed discussion of the health effects caused by 1,1,1-trichloroethane see Section 3.2.

3.9 INTERACTIONS WITH OTHER CHEMICALS

Although there are no reports of chemical interactions in humans, several animal studies have identified possible interactions between 1,1,1-trichloroethane and other chemicals.

Ethanol, when given orally to mice at doses of 0.125–2.0 g/kg, potentiated both the lethality and behavioral effects (inverted screen test) of inhaled 1,1,1-trichloroethane at concentrations ranging from ≈200 to 10,000 ppm (Woolverton and Balster 1981). In another study, a 3-day pretreatment of mice with ethanol enhanced 1,1,1-trichloroethane-induced liver toxicity, as indicated by an assay of liver function (bromosulfophthalein retention in plasma), but not an assay of liver damage (SGPT levels) (Klaassen and Plaa 1966). Other studies, using only serum enzyme levels to assay liver damage (SGPT or SGOT), found that ethanol markedly and consistently enhanced the hepatotoxicity of more potent chlorinated compounds such as carbon tetrachloride or trichloroethylene, but had no effect on the hepatotoxicity of 1,1,1-trichloroethane (Cornish and Adefuin 1966; Klaassen and Plaa 1967). Ethanol may potentiate the hepatotoxicity of chlorinated alkanes because of its ability to induce cytochrome P450IIE1 (Ikatsu and Nakajima 1992). The available data indicate that ethanol can enhance the acute neurobehavioral effects of 1,1,1-trichloroethane, but will not cause 1,1,1-trichloroethane to produce severe liver damage (necrosis) like that caused by other chlorinated alkanes such as carbon tetrachloride or 1,1,2-trichloroethane.

Co-exposure of control or ethanol-treated rats to inhaled concentrations of 10 ppm carbon tetrachloride and 200 ppm 1,1,1-trichloroethane did not produce changes in several indices of liver damage (SGPT, SGOT, and liver malondialdehyde) compared with exposure to 10 ppm carbon tetrachloride alone (Ikatsu and Nakajima 1992). This indicates that 1,1,1-trichloroethane may be protective against hepatotoxic effects of cytotoxic haloalkanes. In contrast, co-exposure of ethanol-treated rats to 10 ppm carbon tetrachloride and 10–50 ppm chloroform produced liver damage that was greater than the additive effects of exposure to each component alone; this synergistic interaction was not observed in rats fed a diet without ethanol (Ikatsu and Nakajima 1992). Extrapolation of these results to humans suggests that

heavy drinkers exposed to mixtures of carbon tetrachloride and chloroform may have a greater risk of developing liver damage than those exposed to either chlorinated alkane alone. The results, however, provide no evidence for a synergistic interaction between carbon tetrachloride and 1,1,1-trichloroethane that would enhance the hepatotoxicity of either compound. In experiments with isolated rat hepatocytes, concomitant exposure to chloroform, but not co-exposure to 1,1,1-trichloroethane, potentiated carbon tetrachloride-induced lipid peroxidation (Kefalas and Stacey 1991).

Ketones and ketogenic substances (i.e., substances metabolized to ketones or that produce ketosis in the body) potentiate the hepatotoxicity of certain chlorinated alkanes including carbon tetrachloride, chloroform, and 1,1,2-trichloroethane (Plaa 1988). Although the mechanism of this potentiation is not fully understood, Plaa (1988) has proposed enhanced bioactivation of the toxicant through cytochrome P-450 induction. Studies with mice, however, found that treatment with acetone or isopropanol (which is metabolized to acetone) did not enhance the hepatotoxicity of 1,1,1-trichloroethane, but enhanced the threshold doses of chloroform, 1,1,2-trichloroethane, and trichloroethylene to elevate SGPT (Traiger and Plaa 1974). Single intraperitoneal doses of 1,1,1-trichloroethane (1.0 mL/kg) did not produce liver damage (assayed either as elevation in SGPT or in concentrations of liver triglycerides) in control mice or in mice with alloxan-induced diabetes (i.e., that were in a state of ketosis) (Hanasono et al. 1975). Other studies examining the influence of agents that enhance cytochrome P-450 metabolism have provided mixed results. The cytochrome P-450 mixed-function oxidase inducer, phenobarbital, enhanced the hepatotoxicity of 1,1,1-trichloroethane in the rat study by Carlson (1973) but not in that of Cornish et al. (1973). In general, the available data suggest that ketones, ketogenic substances, or cytochrome P-450 inducers will not potentiate 1,1,1-trichloroethane hepatotoxicity.

Concurrent injections of nicotine potentiate the lethality produced by intraperitoneal injection of 1,1,1-trichloroethane in mice (Priestly and Plaa 1976). Although no explanation has been given for the effect of nicotine, stimulation of the sympathetic nervous system and release of epinephrine from the adrenal medulla might enhance cardiac arrhythmias.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to 1,1,1-trichloroethane than will most persons exposed to the same level of 1,1,1-trichloroethane 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 1,1,1-trichloroethane, or compromised function of organs affected by 1,1,1-trichloroethane. Populations who are at greater risk due to their unusually high exposure to 1,1,1-trichloroethane are discussed in Section 6.7, Populations With Potentially High Exposures.

Limited data from animal studies (Woolverton and Balster 1981) indicate that alcohol drinkers may be more susceptible to the acute neurobehavioral effects of 1,1,1-trichloroethane. Moderate to heavy alcohol drinkers may be more susceptible to the hepatotoxicity of some chlorinated alkanes, such as carbon tetrachloride, chloroform, and 1,1,2-trichloroethane, due to ethanol induction of hepatic cytochrome P-450 isozymes involved in the activation of these compounds to intermediate hepatotoxic metabolites. Available animal studies (Cornish and Adefuin 1966; Klaassen and Plaa 1966, 1967), however, have not demonstrated that ethanol ingestion will potentiate the hepatotoxicity of 1,1,1-trichloroethane. Furthermore, evidence indicates that ethanol does not cause 1,1,1-trichloroethane and carbon tetrachloride to interact synergistically to produce hepatotoxic effects, although such an interaction has been demonstrated for ethanol, carbon tetrachloride, and chloroform (Ikatsu and Nakajima 1992). The available data suggest that alcohol ingestion is not likely to significantly potentiate the hepatotoxicity of 1,1,1-trichloroethane.

Diabetics consistently in a state of ketosis may be more susceptible to the hepatotoxicity of certain chlorinated alkanes including carbon tetrachloride, chloroform, and 1,1,2-trichloroethane, due to a potentiation from increased ketone levels in the body. Animal studies indicate that the ketone potentiation of the hepatotoxicity of chlorinated alkanes involves an enhancement of the metabolic production of hepatotoxic intermediate metabolites. Available data, however, indicate that ketones do not appreciably potentiate the hepatotoxicity of 1,1,1-trichloroethane (Plaa 1986, 1988). Thus, diabetics in a state of ketosis are not likely to be more susceptible to the hepatotoxicity of 1,1,1-trichloroethane than the population at large.

Because 1,1,1-trichloroethane is associated with some cardiovascular effects (see Section 3.2.1.2), persons with compromised heart conditions may be at additional risk around high exposure levels of 1,1,1-trichloroethane and should be restricted to some lower level of exposure.

Although no data are available that address this issue, it is possible that individuals with impaired respiratory function (e.g., emphysema, poor perfusion) might excrete less 1,1,1-trichloroethane in a given

period than other people, since most of a single dose is expired (Monster et al. 1979; Nolan et al. 1984). In situations of prolonged exposure, such as living near a hazardous waste site, this might contribute to accumulation of 1,1,1-trichloroethane in the body. People with respiratory disease might, therefore, constitute a more susceptible population.

Young people might be unusually susceptible to 1,1,1-trichloroethane, since the nervous system continues to develop in humans after birth and this chemical may produce residual neurological effects. Developmental toxicity data in humans are not available to address this question. Neurobehavioral testing of exposed rat pups was negative in one study (York et al. 1982). Delays in developmental milestones (pinnae detachment, incisor eruption, and eye opening) and impaired performance in neurobehavior tests were noted in mouse pups of dams exposed to 1,1,1-trichloroethane during later stages of gestation at levels that did not result in apparent maternal toxicity (Jones et al. 1996). These results suggest that developing organisms may be more susceptible than adults to the toxic effects of 1,1,1-trichloroethane. However, Jones et al. (1996) reported delays in developmental milestones (pinnae detachment, incisor eruption, and eye opening) and impaired neurobehavioral performance in mouse pups of dams exposed to 1,1,1-trichloroethane during later stages of gestation. These results indicate that children might be more susceptible to 1,1,1-trichloroethane than adults.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to 1,1,1-trichloroethane. 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 1,1,1-trichloroethane. 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 halogenated hydrocarbon solvents, such as 1,1,1-trichloroethane:

Ellenhorn MJ, Schonwald S, Ordog G, et al., eds. 1997. Medical toxicology: Diagnosis and treatment of human poisoning. 2nd edition. Baltimore, MD: Williams & Wilkins, 1436-1440.

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

Ingested 1,1,1-trichloroethane is rapidly absorbed by the gastrointestinal tract of humans and animals (Mitoma et al. 1985; Reitz et al. 1988; RTI 1987; Stewart and Andrews 1966). To minimize absorption following ingestion, several treatments have been suggested, including administration of milk or water to dilute the gastrointestinal tract contents, gastric lavage, and administration of emesis-inducing compounds or activated charcoal (Goldfrank et al. 1990; Stutz and Janusz 1988). Butter or some other food high in lipids might be given. The lipids will serve to delay substantially, and possibly diminish, systemic absorption of 1,1,1-trichloroethane. It should be noted, however, that upon induction of emesis, there is the possibility of aspiration of 1,1,1-trichloroethane into the lungs, which may result in pneumonia. Therefore, treatment via stomach pump has been recommended. Due to rapid absorption of 1,1,1-trichloroethane by the gut, any measures to retard absorption must be taken very rapidly.

Inhaled 1,1,1-trichloroethane is rapidly absorbed and expired, predominantly unchanged, through the lungs (see Section 3.4.). The rapidity with which inhaled 1,1,1-trichloroethane is absorbed (Astrand et al. 1973; Morgan et al. 1972a, 1972b) indicates that assisted ventilation or positive pressure ventilation techniques will not prevent the absorption of 1,1,1-trichloroethane in the lung and emphasizes the importance of removing the subject from the contaminated atmosphere. Nevertheless, such techniques have been suggested to help eliminate the compound from the body (Bronstein and Currance 1988).

The volatility of 1,1,1-trichloroethane is likely to limit absorption of the dermally applied compound, even though dermal absorption under conditions that prevent evaporation is rapid and extensive (Fukabori et al. 1977; Morgan et al. 1991; Stewart and Dodd 1964; Tsuruta 1975). Washing the skin with soapy water has been suggested to reduce the absorption of dermally applied 1,1,1-trichloroethane (Bronstein and Currance 1988; Goldfrank et al. 1990; Stutz and Janusz 1988). Ethyl or isopropyl alcohol also could be used to dilute 1,1,1-trichloroethane on the skin. Flushing the exposed eye with large quantities of water or saline for 15–30 minutes has been suggested to prevent absorption and soothe irritation (Bronstein and Currance 1988; Stutz and Janusz 1988).

3.11.2 Reducing Body Burden

When exposure to 1,1,1-trichloroethane ceases, regardless of route of exposure, the compound is rapidly cleared from the body, predominantly by exhalation of unchanged 1,1,1-trichloroethane in expired air (see

Section 3.4.). Very little metabolism of the compound takes place, and despite a preferential distribution of absorbed 1,1,1-trichloroethane to fatty tissues, significant retention does not occur without continued exposure. Thus, continued ventilation by the lungs will eliminate the compound from the body. Suggested methods to assist in lung ventilation include orotracheal and nasotracheal intubation for airway control and positive pressure ventilation techniques (Bronstein and Currance 1988; Ellenhorn and Barceloux 1988).

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

Suggested methods to treat the effects of acute exposure to 1,1,1-trichloroethane are primarily supportive, rather than active, and are not generally directed against a particular mechanism of action (Bronstein and Currance 1988; Ellenhorn and Barceloux 1988; Ellenhorn et al. 1997; Goldfrank et al. 1990; Herd et al. 1974; Stutz and Janusz 1988; Parraga and West 1998). Suggested methods of treatment include removing the subject from the source of exposure, ventilation assistance, gastric dilution and lavage for ingested material, oxygen administration, and skin washing. Continuous cardiac monitoring is routine for exposed patients. These methods rely on the body's ability to eliminate rapidly 1,1,1-trichloroethane and its metabolites. Mechanisms of action, however, are discussed in this section in relation to the possible development of interfering treatment methods.

The mechanism by which 1,1,1-trichloroethane and other organic solvents depress the central nervous system is poorly understood, but is thought to involve interactions of the parent compound with lipids and/or proteinaceous components of neural membranes (Evans and Balster 1991). No known methods specifically counteract the central nervous system effects of 1,1,1-trichloroethane. Because the specific cellular or biochemical nature of central nervous system depression is poorly understood, it is difficult to propose any method to interfere with this effect of 1,1,1-trichloroethane, other than to prevent further exposure to the compound so that it can be cleared from the body.

The acute cardiotoxic effects of 1,1,1-trichloroethane (reduced blood pressure and increased sensitization to epinephrine-induced arrhythmias) appear to be mediated by the compound and not its metabolites (Carlson 1973; Toraason et al. 1990, 1992) and have been associated with the ability of 1,1,1-trichloroethane to interfere with membrane-mediated processes including calcium mobilization during myocardial contraction (Herd et al. 1974; Hoffman et al. 1992; Toraason et al. 1990) and gap junction communication between myocardial cells (Toraason et al. 1992). The administration of epinephrine to counteract

1,1,1-trichloroethane-induced cardiovascular depression has been cautioned against, because of the risk of arrhythmias and ventricular fibrillation (Bronstein and Currance 1988; Goldfrank et al. 1990; Herd et al. 1974). Herd et al. (1974) demonstrated that intravenous injection or infusion of calcium (as calcium gluconate) or phenylephrine protected against 1,1,1-trichloroethane-induced blood pressure reduction in anesthetized dogs and suggested more detailed study to assess whether these compounds could be used routinely to resuscitate exposed individuals. Exogenous calcium appears to counteract the influence of 1,1,1-trichloroethane on calcium mobilization during myocardial contraction (Herd et al. 1974; Hoffman et al. 1992; Toraason et al. 1990). Evidence indicates that phenylephrine counteracts 1,1,1-trichloroethane-induced vasodilation without influencing myocardial function (Herd et al. 1974). Further studies examining these active methods of treatment were not located.

Unlike more potent chlorinated alkanes such as carbon tetrachloride or 1,1,2-trichloroethane, it is not clear whether the hepatotoxicity of 1,1,1-trichloroethane is due to a metabolite or the parent compound (see Section 3.5). If metabolites produced by cytochrome P-450 oxidation or dechlorination are responsible for the hepatotoxicity, administering cytochrome P-450 inhibitors (e.g., SKF-525A) may inhibit the development of toxic effects on the liver. Clinical or animal studies examining the use of such an approach and the possibility of side effects, however, were not located.

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 1,1,1-trichloroethane 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 1,1,1-trichloroethane.

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 1,1,1-Trichloroethane

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to 1,1,1-trichloroethane are summarized in Figure 3-6. The purpose of this figure is to illustrate the existing information concerning the health effects of 1,1,1-trichloroethane. 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.

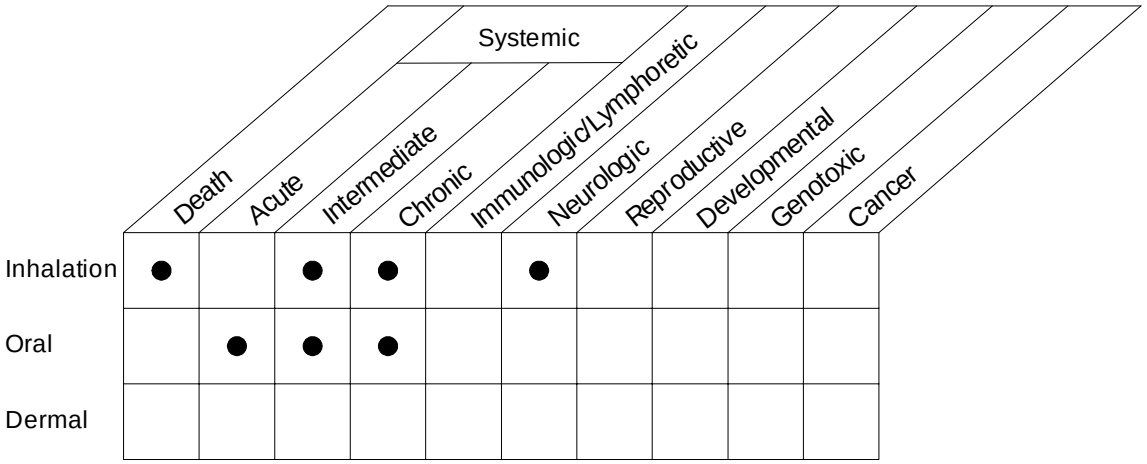
Several case studies have documented the lethality of high concentrations of inhaled 1,1,1-trichloroethane. Experimental studies, as well as case reports, have reported on acute systemic and neurological effects. Chronic systemic, neurological, developmental, and reproductive effects have been investigated in epidemiology studies. Health effects caused by other routes of administration have not been as well studied in humans. One case study regarding oral exposure to 1,1,1-trichloroethane reported acute systemic effects and investigated potential neurological effects. Developmental effects and cancer from exposure to drinking water were investigated by epidemiology studies. The effects of dermal exposure are discussed in case reports regarding peripheral neuropathy and dermal sensitization in workers and in controlled studies regarding skin irritation.

As indicated in Figure 3-6, many aspects of the health effects resulting from inhalation, ingestion, and dermal exposure to 1,1,1-trichloroethane have been studied in animals. Except for genotoxicity, each of the end points has been investigated in animals exposed to 1,1,1-trichloroethane by the inhalation and oral routes. Fewer end points have been studied following dermal exposure.

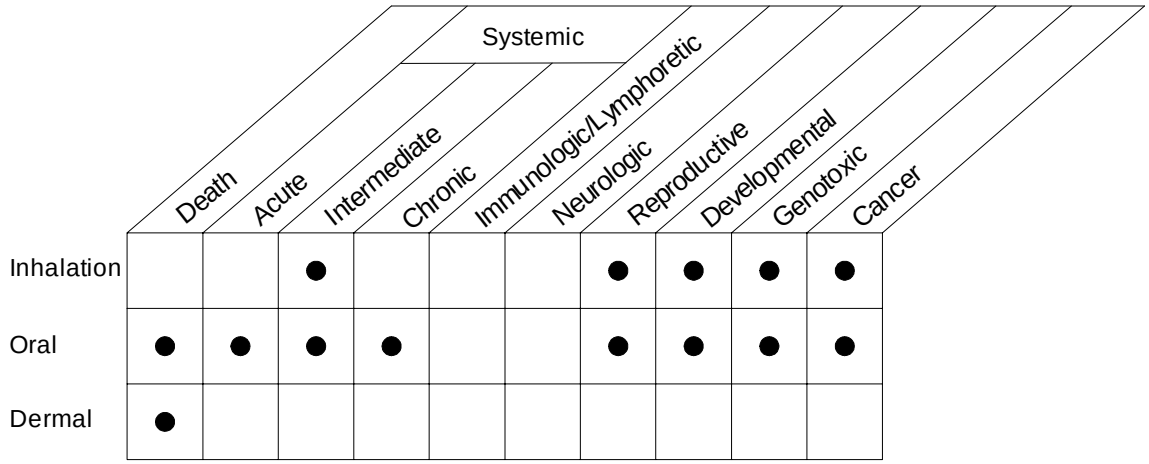
3.12.2 Identification of Data Needs

Acute-Duration Exposure. The primary target organs of 1,1,1-trichloroethane toxicity have been identified from human and animal studies. The central nervous system appears to be the most sensitive

Figure 3-6. Existing Information on Health Effects of 1,1,1-Trichloroethane



Human



Animal

● Existing Studies

target organ after inhalation exposure. Decreased psychomotor performance, altered EEG, ataxia, and anesthesia have been observed in humans after inhalation exposure (Dornette and Jones 1960; Gamberale and Hultengren 1973; Mackay et al. 1987; Muttray et al. 2000; Sot et al. 1975; Stewart et al. 1961, 1969; Torkelson et al. 1958). Cardiovascular effects (decreased blood pressure and arrhythmias) and mild hepatic effects (increased serum enzyme levels, fatty liver, cholestasis) have also been observed (Cohen and Frank 1994; Croquet et al. 2003; Dornette and Jones 1960; Guberan et al. 1976; Halevy et al. 1980; Hodgson et al. 1989; Krantz et al. 1959; MacDougall et al. 1987; Stewart 1971; Stewart et al. 1961; Texter et al. 1979; Travers 1974). Developmental toxicity studies in rats and rabbits indicated that 1,1,1-trichloroethane can cause mild developmental delays and effects in the offspring at high levels (usually accompanied by significant maternal toxicity) (BRRC 1987a, 1987b; Jones et al. 1996; York et al. 1982). Acute oral studies have determined lethal levels in animals and have shown that ingested 1,1,1-trichloroethane produces neurological effects and reduced body weight gain in animals, and perhaps mild liver effects as well (Bruckner et al. 2001; Spencer et al. 1990; Torkelson et al. 1958; Tyson et al. 1983). The only human data on ingested 1,1,1-trichloroethane was a single case report (Stewart and Andrews 1966). The distribution of 1,1,1-trichloroethane to the central nervous system after oral administration has not been investigated, but is likely to be similar to that following inhalation exposure. In an oral study of rats and mice, however, a significant concentration of 1,1,1-trichloroethane or its metabolites was found in the liver, a possible target organ (RTI 1987). Data from dermal studies indicate only that concentrated 1,1,1-trichloroethane is a skin irritant (Duprat et al. 1976; Stewart and Dodd 1964; Torkelson et al. 1958; Wahlberg 1984a, 1984b). Pharmacokinetic data based on dermal exposures are limited; however, 1,1,1-trichloroethane is absorbed following dermal exposure (Fukabori et al. 1977; Kezic et al. 2000, 2001; Stewart and Dodd 1964; Tsuruta 1975). Therefore, the central nervous system and the liver are likely to be target organs after sufficient dermal exposure, although doses required to produce effects would be difficult to predict. Data from inhalation studies in humans were sufficient to derive an acute-duration inhalation MRL based on decreased psychomotor performance (Mackay et al. 1987). An acute-duration oral MRL was not derived due to lack of adequate data.

Populations near hazardous waste sites might be exposed to 1,1,1-trichloroethane for brief periods. 1,1,1-Trichloroethane is a frequent contaminant of drinking water supplies, although doses of 1,1,1-trichloroethane ingested by persons living near waste sites are generally significantly lower than doses shown experimentally to cause central nervous system depression or cardiac arrhythmias. Nevertheless, valuable information could be gathered from acute oral animal toxicity studies with neurological and cardiovascular end points. Similarly, acute dermal studies have focused on death and skin irritation, but

have not determined the doses that might produce other effects. This information might be useful because dermal exposure to 1,1,1-trichloroethane is common among workers in certain industries, including those who clean up toxic waste sites. Route-to-route extrapolation of existing inhalation data using PBPK models might be a useful approach to assessing health risk from acute-duration oral or dermal exposure to 1,1,1-trichloroethane. Such models are useful in predicting tissue levels of a given chemical and its metabolites following exposure by various routes.

Intermediate-Duration Exposure. No studies were located regarding intermediate-duration exposure to 1,1,1-trichloroethane in humans. Data from animal studies indicate that the primary target organs of 1,1,1-trichloroethane after intermediate-duration inhalation exposure are the central nervous system and the liver. Behavioral effects, decreased activity, and unconsciousness have been reported in animals (Mattsson et al. 1993; Moser et al. 1985; Torkelson et al. 1958), as have chemical changes indicative of physical damage to the brain (Rosengren et al. 1985). Mild hepatic effects such as increased liver weight and fatty changes also have been reported (Adams et al. 1950; Calhoun et al. 1981; McNutt et al. 1975; Torkelson et al. 1958). Liver necrosis was reported in one study (McNutt et al. 1975). Decreased body weight gain was reported in several studies (Adams et al. 1950; Bruckner et al. 2001; NTP 2000; Prendergast et al. 1967). Reproductive and developmental effects also have been investigated following oral exposure (George et al. 1989; Lane et al. 1982; NTP 1988a, 1988b). Intermediate-duration dermal exposure studies revealed only mild hepatic effects and skin irritation (Torkelson et al. 1958; Viola et al. 1981). Pharmacokinetic data to help identify potential target organs after dermal exposure were not located.

Inhalation data were sufficient to derive an intermediate MRL based on chemical changes suggesting physical damage in the brain of gerbils (Rosengren et al. 1985). Data from the oral study of NTP (2000) were sufficient to derive an acute-duration oral MRL based on reduced body weight gain in female mice. Additional intermediate-duration oral studies could be designed to assess more subtle neurological effects in animals exposed to 1,1,1-trichloroethane via the oral exposure route. Intermediate-duration dermal studies that attempt to determine NOAEL and LOAEL values for systemic and other neurological effects would be valuable, because populations near hazardous waste sites might be exposed to 1,1,1-trichloroethane by this route for intermediate periods. Route-to-route extrapolation of existing inhalation data using PBPK models might be a useful approach to assessing health risk from intermediate-duration oral or dermal exposure to 1,1,1-trichloroethane.

Chronic-Duration Exposure and Cancer. The information provided in the limited number of chronic-duration exposure studies in humans is insufficient to define threshold effect levels. Chronic-duration inhalation and oral studies in animals have not defined threshold effect levels for most end points, although LOAEL values were reported for decreased body weight in rats and mice (Maltoni et al. 1986; NCI 1977; Quast et al. 1988). No studies of chronic-duration dermal exposure in humans or animals were located. Pharmacokinetic studies after acute oral exposure indicate that the liver is a potential target organ; the mild liver effects observed in chronic-duration animal studies are supportive (Quast et al. 1988). Existing pharmacokinetic data, however, are not sufficient to identify other target organs after chronic oral, inhalation, or dermal exposure, even though relatively high exposure levels have been tested.

MRL values were not derived for chronic-duration inhalation exposure studies because target organs could not be identified. Similarly, a chronic oral MRL was not derived due to lack of adequate data.

Because populations near hazardous waste sites might be chronically exposed to 1,1,1-trichloroethane, studies that attempt to determine threshold effect levels for inhalation, oral, and dermal exposure would be valuable.

Two-year cancer bioassays have been performed following both inhalation and oral exposure. The results of one oral study indicate that 1,1,1-trichloroethane may have increased the occurrence of immunoblastic lymphosarcoma in rats (Maltoni et al. 1986). Definite conclusions or implications could not be drawn based on this report, however, since experimental procedures were compromised, only one dose level was used and only a small number of rats responded. Although no effects were found in a well-designed inhalation study at exposure levels ≤1,500 ppm (Quast et al. 1988), a follow-up chronic inhalation bioassay incorporating higher doses, an oral bioassay using several dose levels, larger study groups, and use of more than one species would allow more definitive assessment of 1,1,1-trichloroethane's carcinogenic potential.

Genotoxicity. No studies were located regarding the genotoxic potential of 1,1,1-trichloroethane in humans. Existing genotoxicity studies indicate that 1,1,1-trichloroethane may be weakly mutagenic in *Salmonella* (Gocke et al. 1981; Nestmann et al. 1980, 1984; Simmon et al. 1977) and is able to induce deletions via intrachromosomal recombination in the yeast *Saccharomyces cerevisiae* (Brennan and Schiestl 1998) and transform mammalian cells *in vitro* (Daniel and Dehnel 1981; Hatch et al. 1982, 1983;

Milman et al. 1988; Price et al. 1978; Tu et al. 1985). Numerous tests of other genotoxic effects have mostly been negative; however, only a few of these studies made an effort to prevent loss of 1,1,1-trichloroethane due to volatility. Studies designed to account for this property would allow a more complete assessment of genotoxicity. Valuable information also would be provided by tests of chromosomal aberrations in peripheral lymphocytes from humans known to have been exposed to 1,1,1-trichloroethane. In addition, genotoxicity testing of 1,1,1-trichloroethane metabolites might be useful.

Reproductive Toxicity. An epidemiology study found no relationship between adverse pregnancy outcomes and occupational exposure of fathers to 1,1,1-trichloroethane during spermatogenesis (Taskinen et al. 1989). Limited information regarding reproductive toxicity in animals was located. A multigeneration reproduction study of rats exposed to 1,1,1-trichloroethane in drinking water found no reproductive effects (Lane et al. 1982). Histological evaluation of reproductive organs and tissues after inhalation exposure of rats and mice revealed no lesions attributable to 1,1,1-trichloroethane exposure (Adams et al. 1950; Calhoun et al. 1981; Eben and Kimmerle 1974; Quast et al. 1988; Torkelson et al. 1958; Truffert et al. 1977). However, testicular degeneration was observed in guinea pigs (Adams et al. 1950). Reduced epididymal spermatozoal concentration was noted in male rats and mice administered 1,1,1-trichloroethane in the diet at a concentration of 80,000 ppm (approximate doses of 4,800 and 15,000 mg/kg/day) for 13 weeks, but there were no other indications of adverse male reproductive effects and no signs of altered estrus in similarly-treated female rats and mice (NTP 2000). There are no pharmacokinetic data in humans to help evaluate potential reproductive effects. Reproductive function has not been assessed in animals after inhalation or dermal exposure to 1,1,1-trichloroethane; however, available toxicokinetic data do not suggest route-specific target organs. Nevertheless, an inhalation study of reproductive function in animals would be valuable for assessing reproductive toxicity, since inhalation is the predominant route of exposure for humans to 1,1,1-trichloroethane, and reproductive toxicity of 1,1,1-trichloroethane has not been extensively assessed in humans or animals.

Developmental Toxicity. No relationship between maternal exposure to 1,1,1-trichloroethane and adverse pregnancy outcomes (spontaneous abortions/congenital malformations) was found in human epidemiology studies (Deane et al. 1989; Lindbohm et al. 1990; Swan et al. 1989; Taskinen et al. 1989; Windham et al. 1991; Wrensch et al. 1990a, 1990b). Some studies in animals indicate that 1,1,1-trichloroethane is a potential developmental toxicant in quite high doses. Minor skeletal anomalies (delayed ossification and extra ribs in rats and rabbits, respectively, and decreased fetal body weight in rats) have been reported after inhalation exposure of pregnant rats or rabbits during major organogenesis (BRRC

1987a, 1987b; York et al. 1982). These exposures were at concentrations that also produced significant maternal toxicity in two of the studies (BRRC 1987a, 1987b). Delays in developmental milestones (pinnae detachment, incisor eruption, and eye opening) and impaired performance in neurobehavior tests were noted in mouse pups of dams exposed to 1,1,1-trichloroethane vapors during later stages of gestation at levels that did not result in apparent maternal toxicity (Jones et al. 1996). No neurological effects were reported in the offspring of rats gavaged with 1,1,1-trichloroethane during gestation and lactation (Dow Chemical 1993). A multigeneration developmental study of oral 1,1,1-trichloroethane exposure reported no teratogenic effects in rats (Lane et al. 1982). Although developmental studies by the dermal route are lacking, available pharmacokinetic data do not suggest route-specific target organs. Route-to-route extrapolation of existing inhalation and oral data using PBPK models might be a useful approach to assessing the risk of adverse developmental effects from dermal exposure to 1,1,1-trichloroethane.

Immunotoxicity. No studies were located regarding the immunotoxicity of 1,1,1-trichloroethane in humans. Information regarding the lymphoreticular system was limited to reports of spleen congestion in subjects acutely exposed to high levels of 1,1,1-trichloroethane (Gresham and Treip 1983; Stahl et al. 1969). Exposed mice were not more susceptible to bacterial infection than unexposed control mice after a single inhalation exposure to 1,1,1-trichloroethane (Aranyi et al. 1986). Very limited information exists regarding histology and function of tissues of the lymphoreticular system after 1,1,1-trichloroethane exposure by any route. Histological evaluation of lymphoreticular tissues, including lymph nodes, thymus, and spleen, revealed no lesions attributable to 1,1,1-trichloroethane exposure (Adams et al. 1950; Calhoun et al. 1981; Kjellstrand et al. 1985b; Prendergast et al. 1967; Torkelson et al. 1958).

Although available studies do not suggest that 1,1,1-trichloroethane induces immunotoxicity, comprehensive immunotoxicity assessments have not been performed. Therefore, an acute- or intermediate-duration exposure study including a comprehensive evaluation of lymphoid tissues and blood components would provide valuable information regarding potential immunotoxicity.

Neurotoxicity. The central nervous system is apparently the primary target organ of 1,1,1-trichloroethane toxicity. Behavioral effects, altered EEG recordings, ataxia, unconsciousness, and death have been reported in human and animal studies (Halogenated Solvents Industry Alliance 1991; Balster et al. 1982, 1997; Bowen and Balster 1996, 1998; Bruckner et al. 2001; Clark and Tinston 1982; DeCeaurriz et al. 1983; del Amo et al. 1996; Dornette and Jones 1960; Evans and Belster 1993; Gamberale and Hultengren 1973; Garnier et al. 1991; Gehring 1968; Kelafant et al. 1994; Mackay et al. 1987; Mattsson et al. 1993;

Moser and Balster 1985, 1986; Muttray et al. 2000; Páez-Martínez et al. 2003; Spencer et al. 1990; Stewart et al. 1961, 1969; Sullivan 1994; Torkelson et al. 1958; Warren et al. 1997, 1998; Wiley et al. 2002; Winek et al. 1997; Woolverton and Balster 1981; You et al. 1994). Neurochemical changes following prolonged inhalation exposure, suggesting morphological damage to the brain, have been reported in gerbils (Rosengren et al. 1985). Respiratory depression appears to cause death in humans and animals. Most studies were conducted by inhalation exposure, but limited data on oral exposure were also available, including a recent study in which no neurological effects were reported in the offspring of rats treated during gestation and lactation (Dow Chemical 1993) (see Developmental Toxicity). Neurological effects have not been reported after dermal exposure.

Additional in-depth studies of the effects of 1,1,1-trichloroethane on neurological structure and function might provide important information regarding the mechanisms and reversibility of 1,1,1-trichloroethane-induced neurological dysfunction. Studies to follow-up on the reported changes in GFA protein following 1,1,1-trichloroethane exposure may be helpful. Acute-, intermediate-, and chronic-duration exposure studies by the oral route, including comprehensive histological evaluations and nervous system function tests, would provide information regarding the dose-response relationship for this route of exposure. An acute-duration dermal exposure to assess the potential for neurotoxicity by this route would also be useful, although toxicokinetic data available do not suggest route-specific target organs. Route-to-route extrapolation of existing inhalation and oral data using PBPK models might be a useful approach to assessing the risk of adverse neurological effects from dermal exposure to 1,1,1-trichloroethane. Populations residing near hazardous waste sites or in occupational settings might be exposed to 1,1,1-trichloroethane. Well-designed and controlled epidemiology studies of these populations may provide useful information on the potential for 1,1,1-trichloroethane at relevant exposure levels to produce neurological disturbances in humans.

Epidemiological and Human Dosimetry Studies. Epidemiology studies have investigated the relationship between long-term exposure to 1,1,1-trichloroethane and systemic, neurological, reproductive, developmental, and cancer effects in humans, but no health effects associated with exposure have been reported. These studies, however, are limited in design and scope and do not provide definitive conclusions regarding the health effects of 1,1,1-trichloroethane exposure. More extensive studies might provide a definitive assessment of the health hazards of chronic 1,1,1-trichloroethane exposure in humans, especially for occupationally exposed populations. If such effects are identified, human dosimetry studies may be able to correlate 1,1,1-trichloroethane levels in human tissues or fluids with chronic health effects.

The usefulness of such studies on individuals living near hazardous waste sites is questionable since exposure is relatively low and the half-life of 1,1,1-trichloroethane and its metabolites too short. Acute experimental studies in humans have established inhalation exposure levels associated with acute neurological effects. Subpopulations potentially exposed to 1,1,1-trichloroethane include people residing near hazardous waste sites where the chemical is stored, people who encounter it in the workplace (either in its manufacture or application), and people who use household products that contain it. It should be mentioned, however, that as a result of Title VI of the Clean Air Act, potential human exposure to 1,1,1-trichloroethane is expected to be gradually reduced (see Chapter 6).

Biomarkers of Exposure and Effect.

Exposure. Known biomarkers of 1,1,1-trichloroethane exposure include blood, breath, and urine levels of the chemical and its two major metabolites, trichloroethanol and trichloroacetic acid. Metabolism of trichloroethylene and perchloroethylene also produces trichloroethanol and trichloroacetic acid; therefore, these metabolites are not unique to 1,1,1-trichloroethane (Monster 1988). Environmental 1,1,1-trichloroethane levels are significantly correlated with the levels in blood, breath, and urine (Hartwell et al. 1987a; Mizunuma et al. 1995; Monster 1986; Wallace et al. 1982, 1984b, 1985, 1987a, 1987b, 1987c). 1,1,1-Trichloroethane is rapidly cleared from the body after exposure (Astrand et al. 1973; Monster et al. 1979; Nolan et al. 1984; Stewart et al. 1961). The two metabolites have a much longer half-life in the body than the parent compound. Therefore, 1,1,1-trichloroethane levels in the blood, breath, and urine may be used as biomarkers only if they are measured during or shortly after exposure. The two metabolites are more useful as biomarkers for a somewhat longer period after exposure. Because 1,1,1-trichloroethane's half-life in the body is short, and because hematological profiles and clinical chemistry parameters are not usually affected, the further development of biomarkers based on easily-obtained biological fluids may not be useful.

Effect. No specific biomarkers of effect for 1,1,1-trichloroethane were located in the literature. The central nervous system is apparently the most sensitive organ in humans and animals, and neurotoxicity (decreased psychomotor performance, ataxia, and unconsciousness) is observed after short-term high-level exposure. Development of specific biomarkers of effect would facilitate medical surveillance, which could lead to early detection of adverse effects.

Absorption, Distribution, Metabolism, and Excretion. The absorption, metabolism, and elimination of 1,1,1-trichloroethane have been studied extensively in humans and animals. Distribution has not been as well studied. 1,1,1-Trichloroethane is rapidly and efficiently absorbed by the lung, skin (under conditions to prevent evaporation), and gastrointestinal tract of humans and animals (Astrand et al. 1973; Fukabori et al. 1977; Kezic et al. 2000, 2001; Monster et al. 1979; Nolan et al. 1984; Reitz et al. 1988; RTI 1987; Stewart and Andrews 1966; Stewart and Dodd 1964; Tsuruta 1975). As duration of inhalation exposure increases in humans and animals, the percentage net absorption decreases, because steady-state levels are approached in the blood and tissues, and 1,1,1-trichloroethane is metabolized at a low rate. A study with humans equipped with respirators indicated that, during exposure to 1,1,1-trichloroethane vapors in the atmosphere, absorbed doses from inhaled 1,1,1-trichloroethane are much larger than doses from dermal absorption (Riihimaki and Pfaffli 1978). Animal studies demonstrated that, once absorbed, 1,1,1-trichloroethane is distributed by the blood to tissues and organs throughout the body, including developing fetuses, with preferential distribution to fatty tissues (Holmberg et al. 1977; Katagiri et al. 1997; Schumann et al. 1982a; Takahara 1986b). Human data regarding the compound's distribution consist of observations that detectable levels were found in subcutaneous fat, kidney fat, liver, lung, and muscle in 30 autopsy cases (Alles et al. 1988). The predominant pathway of 1,1,1-trichloroethane elimination by humans and animals, regardless of exposure route, is exhalation of the unchanged compound (Mitoma et al. 1985; Monster et al. 1979; Nolan et al. 1984; Reitz et al. 1988; RTI 1987; Schumann et al. 1982a, 1982b). When exposure ceases, the compound rapidly clears from the body. Only trace amounts of the compound remained in animal tissues within days of short-term exposure. Further studies in humans regarding extent and rates of absorption and elimination with dermal exposure to aqueous 1,1,1-trichloroethane solutions or suspensions under conditions allowing evaporation from the skin may provide useful information on dermal contact with contaminated water.

Experiments with animals and humans have demonstrated that only small fractions of absorbed 1,1,1-trichloroethane doses (<10%) are metabolized, regardless of the exposure route (Mitoma et al. 1985; Monster et al. 1979; Nolan et al. 1984; Schumann et al. 1982a, 1982b). 1,1,1-Trichloroethane is metabolized oxidatively to trichloroethanol and trichloroacetic acid by a concentration-dependent, saturable process that appears to involve the cytochrome P-450 mixed-function oxidase system. These metabolites have been detected in urine excreted from exposed humans and animals; other minor metabolites (CO_2 and acetylene, the latter formed by the reductive dechlorination of 1,1,1-trichloroethane under conditions of low oxygen supply) are eliminated in expired air.

The hepatotoxicity of 1,1,1-trichloroethane is quite low compared to other chlorinated hydrocarbons, including 1,1,2-trichloroethane. The relatively low toxicity of 1,1,1-trichloroethane may be due to its relatively low metabolism rate, since the more hepatotoxic halocarbons are extensively metabolized. Whether the mild effects of repeated 1,1,1-trichloroethane exposure are evoked by the parent compound or the limited quantities of metabolites produced is not known, however. The available data indicate that the acute effects on central nervous and cardiovascular systems are caused by 1,1,1-trichloroethane and not its metabolites. The interference of 1,1,1-trichloroethane with membrane-mediated processes, due to lipophilicity, may be responsible for the acute effects on these systems; several cellular and biochemical processes appear to be affected by 1,1,1-trichloroethane.

Comparative Toxicokinetics. The toxicokinetic pattern of 1,1,1-trichloroethane is qualitatively similar in humans, rats, and mice. There are major quantitative differences, however, including a higher blood:air partition coefficient, higher respiratory and circulatory rates, and increased rate of metabolism in mice. This comparison has led to a suggestion that rats may be a better model for humans than mice. Physiologically-based pharmacokinetic models have been developed to describe the kinetic behavior of 1,1,1-trichloroethane in mice, rats, and humans; these models have been used to make interspecies and interroute extrapolations in estimating 1,1,1-trichloroethane exposure levels in humans that will produce (or not produce) toxic effects (Bogen and Hall 1989; Dallas et al. 1989; Dobrev et al. 2001, 2002; Leung 1992; Nolan et al. 1984; Poet et al. 2000; Reitz et al. 1988; USAF 1990). Further research verifying the metabolic constants and other input parameters (partition coefficients, tissue values and blood flows, cardiac output, and respiratory volumes) used in these models might improve the accuracy and utility of the models in interspecies extrapolations. In addition, verification of the models should also be performed at lower doses than those used to calibrate them.

Methods for Reducing Toxic Effects. Suggested methods to treat the effects of acute exposure to 1,1,1-trichloroethane and other halogenated hydrocarbons are generally supportive and rely on the body's ability to eliminate rapidly 1,1,1-trichloroethane and its metabolites. Animal studies indicate that intravenous injection or infusion of calcium gluconate or phenylephrine are protective against acute blood pressure reduction caused by exposure to 1,1,1-trichloroethane (Herd et al. 1974). Further animal testing is needed to assess whether these compounds might be used to resuscitate individuals exposed to high concentrations of 1,1,1-trichloroethane.

Children's Susceptibility. No information was located regarding potential age-related differences in susceptibility to 1,1,1-trichloroethane in humans. Delays in developmental milestones and impaired performance in neurobehavior tests in mouse pups of dams exposed to 1,1,1-trichloroethane vapors during later stages of gestation (Jones et al. 1996) indicate that developing organisms may be more susceptible than adults to the toxic effects of 1,1,1-trichloroethane. Additional well-designed animal studies should be performed to adequately assess the potential for age-related increased susceptibility to 1,1,1-trichloroethane.

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

Two ongoing studies pertaining to 1,1,1-trichloroethane were located in a search of the Federal Research in Progress database (FEDRIP 2004).

Dr. S. Bowen of Wayne State University in Detroit, Michigan has designed experiments to characterize subjective and psychomotor effects of toluene and 1,1,1-trichloroethane. The research includes comparison of the results with those of other abused inhalants. Other experiments are designed to elucidate basic mechanisms underlying and controlling inhalant abuse.

Dr J. Zacny of the University of Chicago, Chicago, Illinois is developing a human laboratory model of inhalant abuse by studying potential determinants of abuse liability of inhalants (including 1,1,1-trichloroethane) in healthy volunteers.

4. CHEMICAL AND PHYSICAL INFORMATION

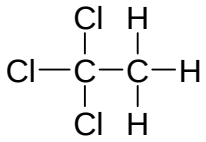
4.1 CHEMICAL IDENTITY

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

4.2 PHYSICAL AND CHEMICAL PROPERTIES

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

Table 4-1. Chemical Identity of 1,1,1-Trichloroethane

Characteristic	Information	Reference
Chemical name	1,1,1-Trichloroethane	CAS 2004
Synonyms(s)	Methylchloroform	CAS 2004
	Methyltrichloromethane	CAS 2004
	1,1,1-TCE	
	Trichloromethylmethane	
	α-Trichloromethane	
Registered trade name(s)	Chlorothene NU	OHM/TADS 1994
	Aerothene TT	
Chemical formula	CCl_3CH_3	CAS 2004
Chemical structure		
Identification numbers:		
CAS registry	71-55-6	CAS 2004
NIOSH RTECS	KJ2975000	RTECS 2004
EPA hazardous waste	U226, F002	HSDB 2004
OHM/TADS	8100101	OHM/TADS 1994
DOT/UN/NA/IMCO shipping	UN 2831, IMO 6.1	HSDB 2004
HSDB	157	HSDB 2004
NCI	C04626	HSDB 2004

CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

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

Property	Information	Reference
Molecular weight	133.4	CAS 2004
Color	Colorless	Archer 1979; Sax and Lewis 1987
Physical state	Liquid	Merck 1989
Melting point	-30.4 °C	Weast 1988
	-33.0 °C	Archer 1979
Boiling point	74.1 °C	Budavari 1989
Density:		
at 20 °C	1.3390 g/mL	Weast 1988
at 25 °C	1.3299 g/mL	Riddick et al. 1986
at 30 °C	1.32096 g/mL	Riddick et al. 1986
Odor	Ethereal, chloroform-like	Archer 1979; Aviado et al. 1976
Odor threshold:		
Water	No data	
Air	120 ppm	Amoore and Hautala 1983;
	500 ppm	Reist and Rex 1977
Solubility:		
Water at 20 °C	0.1495% (wt/wt)	Horvath 1982
Organic solvent(s)	Soluble in alcohol, ether, chloroform; miscible with other chlorinated solvents, soluble in common organic solvents	Archer 1979; Weast 1988
Partition coefficients:		
Log K_{ow}	2.49	Hansch and Leo 1985
Log K_{oc}	2.03	Friesel et al. 1984
	2.02	Chiou et al. 1979
Vapor pressure at 20 °C	124 mm Hg	Boublik et al. 1984
	16.4 1kPa	Riddick et al. 1986
Henry's law constant:		
at 20 °C	$6.3x10^{-3}$ atm	Chiou et al. 1980
at 30 °C	$17.2x10^{-3}$ atm	Gossett 1987
Autoignition temperature	537 °C	HSDB 2004
Flashpoint	None	Archer 1979
Flammability limits	8–10.5%	Archer 1979
Conversion factors:		
ppm (v/v) to mg/m^3 in air (20 °C)	1 ppm = 5.4 mg/m^3	Chiou et al. 1980
mg/m^3 to ppm (v/v) in air (20 °C)	1 mg/m^3 = 0.185 ppm	
Explosive limits	7.5–12.5% in air	NIOSH 1990

CAS = Chemical Abstracts Services; HSDB = Hazardous Substances Data Bank; NIOSH = National Institute for Occupational Safety and Health; v/v = volume by volume; wt/wt = weight by weight

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

5.1 PRODUCTION

According to the 1990 amendments to the Clean Air Act and the Montreal Protocol, U.S. production of 1,1,1-trichloroethane will be cut incrementally, eventually being completely phased out by January 2002. During the period beginning on January 1, 2002 and ending on January 1, 2005, production of limited amounts of 1,1,1-trichloroethane may be authorized by the Administrator for use in essential applications, or for the export to developing countries (EPA 2004m). The total production volumes of 1,1,1-trichloroethane fell from 720 million pounds in 1992 to 450 million pounds in 1993 (CMR 1995). The demand for 1,1,1-trichloroethane was projected to decline at the rate of -10% per year through 1999 (CMR 1995). Despite the proposed phase-out, 1,1,1-trichloroethane was still being manufactured in the United States in 2002 in a production volume range of >100 to <500 million pounds for 2002 (EPA 2002). Two chemical companies are listed as domestic manufacturers in 2003 (SRI 2003): Vulcan Materials Co. Chemicals Division in Geismer, Louisiana and PPG Industries in Lake Charles, Louisiana. The estimated total production capacity at each of the facilities in 1994 (in millions of pounds) is 350 for PPG's plant in Lake Charles, Louisiana and 160 for Vulcan's plant in Geismar, Louisiana (estimated total capacity of 510 million pounds as of April 1, 2003) (SRI 2003).

Besides the above producers of 1,1,1-trichloroethane, Table 5-1 reports the number of facilities in each state that manufacture and process 1,1,1-trichloroethane, the intended use of the product, and the range of maximum amounts of 1,1,1-trichloroethane stored on site. The data reported in Table 5-1 are derived from the Toxics Release Inventory (TRI) (TRI02 2004). Only certain types of facilities were required to report to the TRI databank of EPA. Hence, this is not an exhaustive list.

The most common method for industrial preparation of 1,1,1-trichloroethane is the reaction of hydrochloric acid with vinyl chloride (obtained from 1,2-dichloroethane) to obtain 1,1-dichloroethane, followed by either thermal or photochemical chlorination. Other methods include the catalyzed addition of hydrogen chloride to 1,1-dichloroethylene, and the direct chlorination of ethane itself, followed by separation from the other products produced (Archer 1979). Commercial grades of 1,1,1-trichloroethane usually contain some inhibitor, such as nitromethane, methyl ethyl ketone, toluene, 1,4-dioxane, butylene oxide, 1,3-dioxolane, or secondary butyl alcohols (Archer 1979; OHM/TADS 1992).

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

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	7, 12
CA	5	100	499,999,999	6, 7, 9, 11, 12
IL	1	1,000	9,999	12
IN	4	0	9,999	1, 2, 3, 5, 7, 9, 12
KS	1	10,000	99,999	12
KY	2	10,000	9,999,999	6, 12
LA	4	0	49,999,999	1, 3, 4, 5, 6, 12, 13
MI	2	1,000	9,999	12
MO	1	10,000	99,999	12
MS	1	1,000	9,999	12
NE	1	10,000	99,999	12
NJ	2	1,000	9,999,999	6, 12
NM	1	1,000	9,999	2, 3, 11
NY	1	0	99	12
OH	4	1,000	999,999	2, 3, 7, 12
PA	1	10,000	99,999	7, 9
SC	1	10,000	99,999	7
TX	4	100	999,999	1, 5, 10, 12
UT	2	10,000	99,999	7, 12
WI	1	0	99	2, 3, 6, 11

Source: TRI02 2004 (Data are from 2002)

[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

5.2 IMPORT/EXPORT

According to the Commerce Department's National Trade Data Bank (NTDB 1994), the following amounts of 1,1,1-trichloroethane (in pounds with kg in parentheses) were exported from the United States during the period 1989–1993: 124.3 million (56.4 million) in 1989; 114.6 million (52.0 million) in 1990; 162.4 million (73.7 million) in 1991; 139.7 million (63.4 million) in 1992; and 75.8 million (34.4 million) in 1993. The amount of 1,1,1-trichloroethane exported has declined since 1991. Because 1,1,1-trichloroethane has been classified as an ozone-depleting chemical, its export and import is regulated by Sections 601–607 of the Clean Air Act. 1,1,1-Trichloroethane may not be imported into the United States; however, under section 604(e) of the Clean Air Act, 1,1,1-trichloroethane may be produced domestically for export to developing countries that are parties to the Montreal Protocol and are operating under article 5 of such Protocol until January 1, 2012 (EPA 2004m). No recent data were found regarding amounts of 1,1,1-trichloroethane exported from the United States.

5.3 USE

1,1,1-Trichloroethane was developed initially as a safer solvent to replace other chlorinated and flammable solvents. The uses of 1,1,1-trichloroethane as of 1995 and percentages of total amount devoted to each use are: hydrochlorofluorocarbon (HCFC) intermediate (60%), vapor degreasing and cold cleaning 25% (through 1995), adhesives 5%, coatings and inks 3%, textiles 2%, and electronics and miscellaneous 5% (CMR 1995). During the period beginning on January 1, 2002 and ending on January 1, 2005, the Administrator may authorize the use of limited amounts of 1,1,1-trichloroethane for essential applications such as medical devices and aviation safety. An example is its use for nondestructive testing for metal fatigue and corrosion of existing airplane engines and airplane parts susceptible to metal fatigue. These applications have no safe and effective substitute available.

1,1,1-Trichloroethane was used as a solvent for adhesives (including food packaging adhesives) and in metal degreasing, pesticides, textile processing, cutting fluids, aerosols, lubricants, cutting oil formulations, drain cleaners, shoe polishes, spot cleaners, printing inks, and stain repellents, among other uses. It was used in industry primarily for cold-cleaning, dip cleaning, bucket cleaning, and vapor degreasing operations of items such as precision instruments, molds, electrical equipment, motors, electronic components and instruments, missile hardware, paint masks, photographic film, printed circuit

boards, generators, switchgears, semiconductors, high vacuum equipment, fabrics, and wigs. It was also used for on-site cleaning of printing presses, food packaging machinery, and molds. 1,1,1-Trichloroethane was also used as a chemical intermediate in the production of hydrochlorofluorocarbons and vinyl chloride. It was formerly used as a food and grain fumigant (Archer 1979; Aviado et al. 1976, 1980; Budavari 1989; Sax and Lewis 1987; Stewart 1983; WHO 1992).

1,1,1-Trichloroethane was used extensively in household products. In a "shopping basket" survey, 1,1,1-trichloroethane was found in 216 of 1,159 common household products chosen as likely to contain solvents at concentrations >0.1% by weight (Sack et al. 1992). In a similar study, 1,1,1-trichloroethane was found in 32 of 67 categories (1,026 brands sampled) of common household products at concentrations >1% by weight; trace amounts were listed in all 67 categories (EPA 1987; Maklan et al. 1987). Some of the several commonly used household items that may contain 1,1,1-trichloroethane are shown in Table 5-2. 1,1,1-Trichloroethane is emitted during use of items prevalent in the average home (Pleil and Whiton 1990; Wallace et al. 1987b).

5.4 DISPOSAL

1,1,1-Trichloroethane has been identified as a hazardous waste by EPA, and disposal of this waste is regulated under the Federal Resource Conservation and Recovery Act (RCRA). Specific information regarding federal regulations on 1,1,1-trichloroethane disposal on land, in municipal solid waste landfills, in incinerators, and during underground injection is available in the Code of Federal Regulations (EPA 1992a, 1992b, 1992c, 1992d). Disposal of 1,1,1-trichloroethane can be accomplished through its destruction in a high temperature incinerator equipped with a hydrochloric acid scrubber. The destruction and removal efficiency (DRE) for 1,1,1-trichloroethane in hazardous wastes must attain 99.99% (Carroll et al. 1992). Potential methods of incineration include liquid injection, rotary kiln, and fluidized bed incineration (Carroll et al. 1992; HSDB 2004). Product residues and sorbent media may be packaged in a 17H epoxy-lined drum, encapsulated in an organic polyester resin, and disposed of at an approved EPA disposal site (OHM/TADS 1992). Other methods that have shown promise for the destruction of 1,1,1-trichloroethane are homogeneous sonochemical treatment for aqueous wastes (Cheung et al. 1991) and a combination of ozonation and ultraviolet treatment for groundwater (Kusakabe et al. 1991). From a laboratory feasibility study, it was concluded that the *in situ* biodegradation of 1,1,1-trichloroethane in soils by methane-oxidizing bacteria was not a viable bioremediation method (Broholm et al. 1991).

Table 5-2. 1,1,1-Trichloroethane in Common Household Products[a]

Product	Concentration (percent w/w)[b]
Adhesive cleaners	0.1–95.0
Adhesives	0.2–121.1
Aerosol spray paint	0.2–1.0
Battery terminal protectors	37.1
Belt lubricants	11.4–72
Brake cleaners	0.4–75.6
Carburetor cleaners	0.2–0.3
Circuit board cleaners	NS
Door spray lubricants	95.6
Drain cleaner (nonacid)	97.8
Electric shaver cleaners	2.5–20.3
Engine degreasers	0.2
Fabric finishes	77.9–85.1
Gasket removers/adhesives	0.2–1.0
General purpose spray degreasers	0.1–71.4
General purpose liquid cleaners	72.7–126.7
Ignition wire driers	24.3–43.6
Lubricants	0.1–104.5
Miscellaneous nonautomotive	12.5–67.5
Miscellaneous automotive	0.3–0.4
Oven cleaners	97
Paint removers/strippers	0.1–25.7
Primers	1.2–61.8
Rust removers	0.7
Silicone lubricants	0.2–91.1
Specialized aerosol cleaners	0.2–83.8
Spot removers	10.5–110.8
Spray shoe polish	11.4–62.3
Stereo/record player cleaners	0.7
Suede protectors	4.8–118.5
Tape recorder cleaners	0.2–101.5
Tire cleaners	0.1–90.3
Transmission cleaner/lubricant	113
TV/computer screen cleaners	0.3
Typewriter correction fluid	6–110
VCR cleaners	97.8
Video disk cleaners	0.6
Water repellents	0.2–116.2
Wood cleaners	12.3–20.4
Woodstain/varnishes/finishes	0.1–21.4

[a]Source: Adapted from Frankenberry et al. 1987; Maklan et al. 1987
[b]Average recovery from spiked samples: 97+13%

w/w = weight per weight

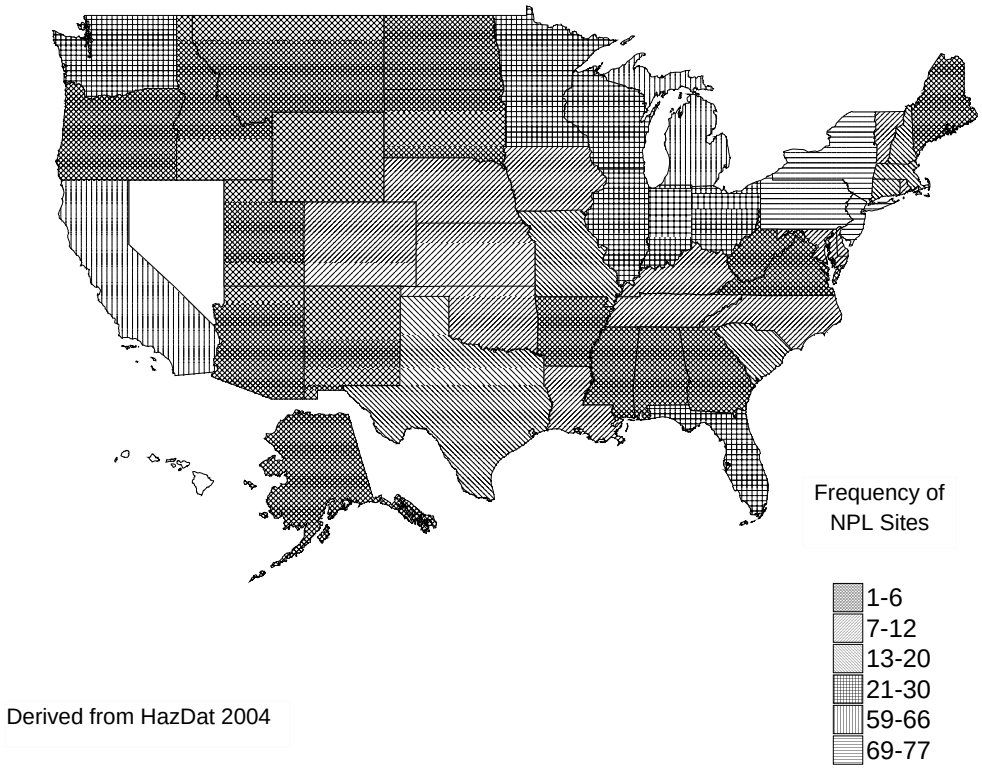
6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

1,1,1-Trichloroethane has been identified in at least 809 of the 1,647 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2004). However, the number of sites evaluated for 1,1,1-trichloroethane is not known. The frequency of these sites can be seen in Figure 6-1. Of these sites, 804 are located within the United States, 3 are located in the Commonwealth of Puerto Rico (not shown), 1 is located in the Virgin Islands (not shown), and 1 is located in Guam (not shown).

1,1,1-Trichloroethane is a synthetic compound that is released to the environment by human industrial activity. It was released to the environment by process and fugitive emissions during its manufacture, formulation, and use in both consumer and industrial products. Because 1,1,1-trichloroethane is volatile and was used as a solvent in many products, it was most frequently found in the atmosphere due to volatilization during production and use. 1,1,1-Trichloroethane is an ozone depleting substance and has been listed as a class I substance under Section 602 of the Clean Air Act. Class I substances have an ozone depletion potential (ODP) of ≥0.2 and include chlorofluorocarbons (CFCs), halons, carbon tetrachloride, 1,1,1-trichloroethane, and methyl bromide. Although recent estimates have yielded an ODP of 0.12 for 1,1,1-trichloroethane, it is still listed as a class I substance. Under Section 604 of the Clean Air Act as amended in 1990, all production and use of 1,1,1-trichloroethane was scheduled to cease as of January 1, 2002. However, 1,1,1-trichloroethaene may still be used for essential applications such as medical devices and aviation safety (for the testing of metal fatigue and corrosion of existing airplane engines and other parts susceptible to corrosion) until January 1, 2005. 1,1,1-Trichloroethane (and other class I substances) may also be produced domestically for export to developing countries as specified in Section 604(e) of the Clean Air Act. This exception to the phase-out is scheduled to end by January 1, 2012 for 1,1,1-trichloroethane (EPA 2004m). 1,1,1-trichloroethane was still being manufactured in the United States in 2002 in a production volume range of >100 – <500 million pounds. More current production data are not yet available and therefore, it is unclear what stage the phase-out is in at this time.

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



6. POTENTIAL FOR HUMAN EXPOSURE

1,1,1-Trichloroethane is no longer used in common household products. The current likelihood of exposure of the general population to 1,1,1-trichloroethane is remote. Possible routes of exposure to 1,1,1-trichloroethane were inhalation, dermal contact, or through the ingestion of either contaminated water or food. Exposure by inhalation was expected to predominate. The general population was exposed to 1,1,1-trichloroethane because of its prevalence in common household products. Indoor air concentrations were determined to be greater than nearby outdoor concentrations, probably as a result of its presence in a myriad of consumer products in the past. Occupational exposure to 1,1,1-trichloroethane could occur by inhalation or dermal contact during its manufacture and formulation, during its use as a cleaner of manufactured components, and during the application of the numerous paints, resins, adhesives, and cleaners containing it as a solvent. At hazardous waste sites, inhalation is expected to be the predominant route of exposure; however, ingestion of contaminated water may occur also.

The dominant environmental fate process for 1,1,1-trichloroethane is volatilization to the atmosphere. Once in the atmosphere, reaction with photochemically-produced hydroxyl radicals is expected to be the most important transformation process for 1,1,1-trichloroethane; the estimated atmospheric lifetime for this process is about 6 years. This long atmospheric lifetime allows about 15% of 1,1,1-trichloroethane to migrate to the stratosphere, where it may be degraded by lower wavelength ultraviolet light, not available in the troposphere, to produce atomic chlorine. The chlorine atoms produced in the stratosphere by this process may react with ozone causing the erosion of the ozone layer. However, direct photochemical degradation of 1,1,1-trichloroethane in the troposphere should not occur. The moderate water solubility of 1,1,1-trichloroethane suggests that rain washout can occur; however, 1,1,1-trichloroethane removed from the atmosphere by this process would be expected to re-volatilize. The lengthy half-life for 1,1,1-trichloroethane in the troposphere allows it to be carried great distances from its original point of release, and it has been found in remote places far from any known source of release.

If released to soil, 1,1,1-trichloroethane should display high mobility and the potential for leaching into groundwater. Volatilization from soil surfaces to the atmosphere is expected to be an important fate process. Although data regarding biodegradation of 1,1,1-trichloroethane in soil are lacking, it is not expected to be an important fate process. 1,1,1-Trichloroethane is not expected to undergo aerobic biodegradation, but there is some experimental evidence that biodegradation may occur under anaerobic conditions.

Once released to surface water, 1,1,1-trichloroethane is expected to undergo volatilization to the atmosphere. Neither adsorption to sediment nor bioconcentration in aquatic organisms is recognized as an important removal process. Aerobic biodegradation of 1,1,1-trichloroethane can occur in the presence of methane-oxidizing bacteria. If released to groundwater, biodegradation of 1,1,1-trichloroethane under anaerobic conditions is known to occur; however, it appears to be a slow process under most environmental conditions.

1,1,1-Trichloroethane may very slowly undergo abiotic degradation in soil or water by elimination of hydrochloric acid (HCl) to form 1,1-dichloroethene, which also can be considered a pollutant, or it can undergo hydrolysis to form the naturally occurring acetic acid. Direct photochemical degradation is not expected to be an important fate process.

6.2 RELEASES TO THE ENVIRONMENT

The manufacture and use of 1,1,1-trichloroethane was scheduled to be phased out by 2002. Since the declines in emissions closely follow the declines in production and use, the emissions of 1,1,1-trichloroethane to the atmosphere should show a corresponding decline (EPA 2004m).

6.2.1 Air

A correlation of data from the EPA Air Toxics Emission Inventory with industrial source codes (SIC codes), shows that volatile emissions of 1,1,1-trichloroethane are associated with 122 different industrial classifications that run the gamut from manufacturing and formulation to secondary uses (Pacific Environmental Services, Inc. 1987). Release of 1,1,1-trichloroethane, in most cases, is an expected result of its use (Spence and Hanst 1978). Small amounts of 1,1,1-trichloroethane is also released to the atmosphere from coal-fired power plants (Garcia et al. 1992), from incineration of hospital wastes (Green et al. 1992; Walker and Cooper 1992), incineration of military nerve agents (Mart and Henke 1992), incineration of industrial wastes containing certain plastics and waste solvents (Nishikawa et al. 1992, 1993), and incineration of municipal waste water sludge (Vancil et al. 1991). 1,1,1-Trichloroethane contained in consumer products was released into the atmosphere during the application, drying, or curing of these products. 1,1,1-Trichloroethane can enter the atmosphere via the air-stripping treatment of waste water. Volatilization, which accounts for ≈100% of removal in waste water, occurs during this process (Kincannon et al. 1983a). Volatilization from waste lagoons is also likely (Shen 1982).

Precise quantitative data on 1,1,1-trichloroethane air emissions are lacking. A large proportion of total production probably found its way into the atmosphere. Estimates for 1984 suggest that 100.4 kilotons (220 million pounds) were released during use by the European Economic Community (EEC) and other western European countries, a figure representing some 70% of total consumption in Europe (Herbert et al. 1986). Global estimates indicate that 1,497 million pounds (679 million kg) of 1,1,1-trichloroethane were released to the atmosphere in 1988 (Midgley 1989). 1,1,1-Trichloroethane releases in air from facilities in each state in the United States that manufactured or processed 1,1,1-trichloroethane during 2002 are reported in the Toxics Release Inventory (TRI) and listed in Table 6-1 (TRI02 2004). According to TRI02 (2004), an estimated total of 234,013 pounds of 1,1,1-trichloroethane, amounting to 85.5% of the total environmental release, was discharged to the air from manufacturing and processing facilities in the United States in 2001. The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list. However, a comparison of TRI data for 1992 and 2002 (115 million pounds and 234,013 pounds, respectively) shows that the nationwide emission of 1,1,1-trichloroethane in the atmosphere has decreased by 97.9% during this period. A 36% reduction in atmospheric emissions was observed in Irvine, California, from 1989 to 1990 (Brown and Hart 1992). Most processes that use 1,1,1-trichloroethane result in some fugitive emissions. For example, the release of 1,1,1-trichloroethane from an industrial solvent recycling facility was 16.7% of the throughput (Balfour et al. 1985).

6.2.2 Water

1,1,1-Trichloroethane can be released to surface water from the waste water of industries in any of the numerous industrial classifications that used or produced this compound. The STORET database for values registered in the years 1980–1988 shows that 1,1,1-trichloroethane tested positive in 12% of effluent samples with maximum, median, and mean concentrations of 6,500, 8.0, and 171 mg/L, respectively (STORET 1988). 1,1,1-Trichloroethane releases in water, including release to publicly owned treatment works (POTW), from facilities in each state in the United States that manufactured or processed 1,1,1-trichloroethane during 2002 are reported in Table 6-1 (TRI02 2004). According to TRI02 (2004), 0.049% of the total 1,1,1-trichloroethane environmental release was discharged to environmental waters from manufacturing and processing facilities in the United States in 2002. The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list. Higher concentrations of 1,1,1-trichloroethane have been found in surface waters near known

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use 1,1,1-Trichloroethane[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	3	592	No data	0	0	0	592	0	592
CA	6	12,057	No data	0	0	0	12,057	0	12,057
IL	2	10	No data	0	198	154	10	352	362
IN	4	284	No data	0	0	0	284	0	284
KS	1	500	No data	0	5	0	500	5	505
KY	2	16,605	6	0	250	0	16,611	250	16,861
LA	4	151,670	46	0	18	0	151,717	17	151,734
MI	2	505	No data	0	38,405	0	38,881	29	38,910
MO	1	3	0	0	0	0	3	0	3
MS	1	500	No data	0	0	0	500	0	500
NE	1	255	No data	0	0	0	255	0	255
NJ	2	111	28	0	27	0	162	4	166
NM	1	6,000	No data	0	250	0	6,000	250	6,250
NY	1	0	No data	0	0	5	0	5	5
OH	4	3,106	5	12	258	0	3,111	270	3,381
PA	1	80	No data	0	0	0	80	0	80
SC	1	470	No data	0	0	0	470	0	470
TX	5	3,317	14	0	0	0	3,331	0	3,331
UT	2	37,937	No data	0	0	0	37,937	0	37,937
WI	2	10	No data	0	0	0	10	0	10
Total	46	234,013	99	12	39,411	159	272,512	1,182	273,694

Source: TRI02 2004 (Data are from 2002)

[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, wastewater 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

industrial sources, such as effluent outfalls or disposal sites, compared to the levels found upstream from these sources (see Table 6-2) (Dreisch et al. 1980; Hall 1984; Kaiser and Comba 1986; Kaiser et al. 1983; Wakeham et al. 1983a).

1,1,1-Trichloroethane has been found in samples from four U.S. cities measured in the National Urban Runoff Program (Cole et al. 1984). 1,1,1-Trichloroethane has been found in the effluent from water treatment plants and municipal waste water (Comba and Kaiser 1985; Corsi et al. 1987; DeWees et al. 1992; Feiler et al. 1979; Lue-Hing et al. 1981; McCarty and Reinhard 1980; Namkung and Rittman 1987; Otson 1987; Pincince 1988; Rogers et al. 1987; Vancil et al. 1991; Young 1978; Young et al. 1983).

1,1,1-Trichloroethane can enter groundwater from various sources. Contamination as a result of industrial activity has occurred (Dever 1986; Hall 1984). Leachate from landfills has percolated into groundwater (Barker 1987; Plumb 1987). The measured soil sorption coefficient (K_{oc}) value of 2.02 (Chiou et al. 1980; Gossett 1987) suggests that 1,1,1-trichloroethane released to soil can leach into groundwater. Measurements of 1,1,1-trichloroethane in drinking water from probability-based population studies (Wallace et al. 1984a, 1987a, 1988), indicate the potential for exposure from drinking water.

6.2.3 Soil

1,1,1-Trichloroethane release on land, including underground injection, from facilities in each state in the United States that manufactured or processed 1,1,1-trichloroethane during 2002 are reported in Table 6-1 (TRI02 2004). According to TRI02 (2004), an estimated total of 39,411 pounds of 1,1,1-trichloroethane, amounting to 14.48% of the total environmental release, was discharged to the land from manufacturing and processing facilities in the United States in 2002. The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

Data on soil contamination by 1,1,1-trichloroethane are lacking in the literature, which is what one would expect based on the TRI02 (2004) data given in Table 6-1. Contamination of soil is possible by direct application of insecticides and rodenticides that contain 1,1,1-trichloroethane as a solvent. Land application of sewage sludge at typical application rates may slightly elevate the level of 1,1,1-trichloroethane in agricultural soil, but the level is not expected to be of environmental concern in the majority of cases (Wilson et al. 1994). The most likely routes for soil contamination are through accidental spills, the contamination of soil by landfill leachates, leaching of contaminated surface waters from

Table 6-2. Detection of 1,1,1-Trichloroethane in Water and Sediments

Media type/location	Sampling dates	Number of Samples	Concentration (ppb)		Reference
			Range	Mean	
Surface water					
Ohio River (Huntington, WV)	1978–1979	22	ND–0.57[a]	NS	Dreisch et al. 1980
Schuylkill Creek (Philadelphia, PA)		33	ND–0.28	NS	
Niagara River	1981	17	ND–0.017[b]	0.007	Kaiser et al. 1983
Lake Ontario		82	ND–0.180	NS	
Lake St. Clair, Canada	1984	64	0–0.112[b]	0.052	Kaiser and Comba 1986
Brazos River, TX	1981–1982	10	ND–0.61[a]	0.1	McDonald et al. 1988
Quinnipiac River (Southington, CT)	1980	5	ND–9.7[a]	2.6	Hall 1984
Valley of the Drums, KT (on-site standing water)	1979	NS	ND–9.4[a]		Stonebraker and Smith 1980
Lang Property, NJ	1985	NS	9[a]		EPA 1987c
Pacific Ocean	1975	NS	0.00062–0.0105[c]		Su and Goldberg 1976
Summit National, OH (NPL site)	1987				EPA 1988n
on-site	3	5–66	13		
off-site	6	ND–29	4.8		
Sediments:					
Lake Pontchartrain, LA	1980	NS	ND–0.01[d]		Ferrario et al. 1985
Pacific Ocean (Los Angeles)	1981	2		<0.5	Young et al. 1983
Detroit River, MI	1982	2	1–2[e]	NS	Fallon and Horvath 1985
Summit National, OH (NPL site) on-site pond sediment	1987	7	50–2,500[f]	670[f]	EPA 1988n
Groundwater:					
CERCLA[g] hazardous waste sites	1981–1984	178	NS		Plumb 1987
Landfill Sites, Ontario, Canada	NS	NS	ND–2.8[a]	NS	Barker 1987
Southington, CT	1980	28	ND–11,000[a]	NS	Hall 1984
New Jersey	1980–1982	315	NS	NS	Fusillo et al. 1985

Table 6-2. Detection of 1,1,1-Trichloroethane in Water and Sediments

Media type/location	Sampling dates	Number of Samples	Concentration (ppb) Range	Mean	Reference
Montgomery County, MD	1983	4	<10–1,600[a]	NS	Dever 1986
Hastings, NE	1984	15	ND–12.1[a]	NS	Fischer et al. 1987
Hastings, NE	1984	15	ND–12.1[a]	NS	Fischer et al. 1987
U.S. cities					
Population <10,000 (random samples)	1981–1982	280	ND–18[a]		Westrick et al. 1984
Population <10,000 (nonrandom)[h]		321	ND–8.2		
Population >10,000 (random samples)		186	ND–3.1		
Population >10,000 (nonrandom)[h]		158	ND–21		
Minnesota[i]	1983	20	ND–470[a]	NS	Sabel and Clark 1984
Lang property, NJ	1985	NS	8,200[a]		EPA 1987c
Marshall landfill, CO[j]	1983	NS	ND–350[a]		EPA 1986b
Forest Waste Disposal Site	1983	NS	130[a]		EPA 1986c
Genesee County, MI[j]					
Palmer, MA PSC Resources, Inc. (NPL site)	1987	NS			
on-site			NS	40,000[k]	Massachusetts Department of Public Health 1989
off-site			NS	3,700[k]	
Idaho National Eng. Lab, IO	1987	112	ND–140[a]		Mann and Knobel 1988
9 Urban land-use studies	1991	208	ND–230[a]	NS	Kolpin et al. 1997
Drinking water:					
Old Love Canal, NY	1978	9	0.010–0.120[b]		Barkley et al. 1980
Bayonne/Elizabeth, NJ	1980				Wallace et al. 1984a

Table 6-2. Detection of 1,1,1-Trichloroethane in Water and Sediments

Media type/location	Sampling dates	Number of Samples	Concentration (ppb)		Reference
			Range	Mean	
home		75	0.03–3.50[l]	0.02	
work		45	0.02–1.60	0.07	
Research Triangle Park, NC					
home		30	0.02–1.90		
work		18	0.02–0.89		
New Jersey	1981		NS–5.3	0.6	Wallace et al. 1987a
	1982		NS–2.6	0.2	
	1983		NS–1.6	0.2	
North Carolina	1982		NS–0.05	0.03	
North Dakota	1982		NS–0.07	0.04	
Los Angeles, CA	February 1984	117	NS	0.15[a]	Wallace et al. 1988
Los Angeles, CA	June 1984	52	NS	0.08[a]	
Contra Costa, CA	May 1984	71	NS	0.09[a]	
Drinking water wells (groundwater):					
Maine	NS	NS	NS–5,440	NS	Burmaster 1982
New York			NS–5,100		
Connecticut			NS–1,600		
New Jersey			NS–965		
Nassau County, NY			NS–310	9	
Suffolk County, NY	1976–1986				
public wells		575	NS–900[a]	16.5	Zaki 1986
private wells		19,000	NS–12,200	23.8	
Wisconsin	1980–1984				Krill and Sonzogni 1986
community wells		1,174	NS		
private wells		617	NS		
Rock River Terrace, IL[j]	1985	NS	NS–3.2		EPA 1986d
South Brunswick, NJ	1977	NS	150–1,500		Althoff et al. 1981
Sewage Sludge					
United States (Site NS)	1978	2	23–99[a]		Feiler et al. 1980
Forest Wate Disposal Site, MI[j]	1983	NS	25[a]		EPA 1986c
Vestal, NY[j]	1985–1986	2	25–47[a]	36[a]	ATSDR 1988
Urban runoff:					

Table 6-2. Detection of 1,1,1-Trichloroethane in Water and Sediments

Media type/location	Sampling dates	Number of Samples	Concentration (ppb)		Reference
			Range	Mean	
Washington, DC; Denver, CO	NS–1982	NS	1.6–10[a]	NS	Cole et al. 1984
Rapid City, SD					
Lake Quinsigamond, MA					
Rain:					
Los Angeles, CA	1982	1		0.069[b]	Kawamura and Kaplan 1983
Beaverton, OR	1982	21	0.128–0.924[m]	0.434	Rasmussen et al. 1983
Snow:					
Mt. Hood, OR	1981–1982	25	0.063–0.128[m]	0.091	Rasmussen et al. 1983
California	1975	2	0.0006–0.0062[c]		Su and Goldberg 1976
Alaska		1	0.027		

[a]Data reported in µg/L; converted to ppb using the conversion factor 1 ppb=1 µg/L
[b]Data reported in ng/L; converted to ppb using the conversion factor 1 ppb=1,000 ng/L
[c]Data reported in pg/mL; converted to ppb using the conversion factor 1 ppb=1,000 pg/mL
[d]Data reported in ng/g; converted to ppb using the conversion factor 1 ppb=1 ng/g
[e]Data reported in mg/kg; converted to ppb using the conversion factor 1 ppb=0.001 mg/kg
[f]Data reported in µg/kg; converted to ppb using the conversion factor 1 ppb=1 µg/kg
[g]Comprehensive Emergency Response, Compensation, and Liability Act
[h]Nonrandom sites were chosen by states/municipalities in an attempt to identify problem areas.
[i]Site near municipal solid waste site
[j]NPL site
[k]Data reported in ppm; converted to ppb using the conversion factor 1 ppb=0.001 ppm
[l]Data reported in ng/mL; converted to ppb using the conversion factor 1 ppb=1 ng/mL
[m]Data reported in ppt; converted to ppb using the conversion factor 1 ppb=1,000 ppt

ND = not detected; NPL = National Priorities List; NS = not specified

treatment/storage lagoons, wet deposition, and possibly by the percolation of contaminated rainwater through soil.

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

1,1,1-Trichloroethane is a volatile organic compound with moderate water solubility (1,500 mg/L at 25 °C) (Horvath 1982). The experimental Henry's law constants measured for this compound range from $6.3x10^{-3}$ to $17.2x10^{-3}$ atm m^3/mol at 25 °C (Chiou et al. 1980; Gossett 1987; Tse et al. 1992); this suggests that volatilization from water should be the dominant fate process. Volatilization of 1,1,1-trichloroethane from water has readily occurred in the laboratory, in the field, and during waste water treatment (Dilling 1977; Dilling et al. 1975; Kincannon et al. 1983b; Piwoni et al. 1986; Wakeham et al. 1983b). Volatilization of 1,1,1-trichloroethane also has occurred from soil and from the groundwater of unconfined aquifers to the soil (Kreamer 1984; Piwoni et al. 1986).

Based on the experimental values for the log octanol/water partition coefficient (K_{ow}), 2.49 (Hansch and Leo 1985), and log K_{oc}, in the range of 2.02–2.26 (Chiou et al. 1979; Friesel et al. 1984; Park and Lee 1993), 1,1,1-trichloroethane would be expected to show high mobility in soil and readily leach into groundwater (Lyman et al. 1990; Swann et al. 1983). In surface waters, 1,1,1-trichloroethane would not be expected to show appreciable adsorption to sediment or suspended organic material. An experimental bioconcentration factor (BCF) of 9 (bluegill sunfish) has been determined for 1,1,1-trichloroethane (Barrows et al. 1980), suggesting that in fish and other aquatic organisms, uptake from water should not be an important fate process.

1,1,1-Trichloroethane has a vapor pressure of 123 mm Hg at 20 °C (see Table 4-2), which means that it exists in the vapor phase in the atmosphere (Eisenreich et al. 1983). Since this compound has moderate water solubility (see Table 4-2), vapor phase 1,1,1-trichloroethane will be removed from the air via washout by rain and transported to the terrestrial surface. It has been identified in rainwater (Jung et al. 1992; Kawamura and Kaplan 1983; Pluemacher and Renner 1993; Rasmussen et al. 1983). 1,1,1-Trichloroethane removed by rain water would be expected to re-volatilize rapidly to the atmosphere. Because of its long half-life of ≈4 years in the atmosphere (see Section 6.3.2.1), tropospheric 1,1,1-trichloroethane will be transported to the stratosphere, where it will participate in the destruction of the ozone layer. It will also undergo long-distance transport from its sources of emissions to other remote

and rural sites. This is confirmed by the detection of this synthetic chemical in forest areas of Northern and Southern Europe and in remote sites (Ciccioli et al. 1993).

6.3.2 Transformation and Degradation

6.3.2.1 Air

The dominant atmospheric fate process for 1,1,1-trichloroethane is predicted to be degradation by interaction with photochemically-produced hydroxyl radicals. Earlier experimental rate constants for this gas-phase reaction ranged from $2.8x10^{-14}$ to $1.06x10^{-14}$ cm^3/mol-sec (20–30 °C) (Butler et al. 1978; Chang and Kaufman 1977; Cox et al. 1976; Crutzen et al. 1978; Howard and Evenson 1976; Jeong et al. 1984). More recent work indicates that this rate constant ranges from $0.95x10^{-14}$ cm^3/mol-sec to $1.2x10^{-14}$ cm^3/mol-sec (Finlayson-Pitts et al. 1992; Jiang et al. 1992; Lancar et al. 1993; Talukdar et al. 1992). 1,1,1-Trichloroethane is degraded via H-atom abstraction to $CCl_3CH_2\cdot$ and reacts with O_2 to yield the peroxy radical ($CCl_3CH_2O_2$) (DeMore 1992; Spence and Hanst 1978). Using an estimated atmospheric hydroxyl (OH·) radical concentration of $5.0x10^5$ mol/cm^3 (Atkinson 1985), the more recent rate constants translate to a calculated lifetime or residence time of ≈6 years. The estimated atmospheric lifetime of 1,1,1-trichloroethane which incorporates all removal processes, was also estimated to be ≈6 years (Prinn et al. 1987; Prinn et al. 1992). This indicates that the predominant tropospheric sink of 1,1,1-trichloroethane is through its reaction with OH radicals.

Photolytic degradation experiments have been performed in the presence of NO and NO_2; 1,1,1-trichloroethane underwent <5% degradation in 24 hours in the presence of NO (Dilling et al. 1976). In a smog chamber experiment in the presence of NO_x, 1,1,1-trichloroethane showed a disappearance rate of 0.1% per hour (Dimitriades and Joshi 1977). Other studies have also concluded that 1,1,1-trichloroethane has low potential to form ozone as a result of photochemical reaction in the presence of NO_x (Andersson-Skoeld et al. 1992; Derwent and Jenkin 1991).

Under laboratory conditions thought to mimic atmospheric smog conditions, direct photochemical irradiation of 1,1,1-trichloroethane in the presence of elemental chlorine was performed. 1,1,1-Trichloroethane was the least reactive and thus the most stable of all chloroethanes under these conditions (Spence and Hanst 1978).

Direct photochemical degradation of 1,1,1-trichloroethane in the troposphere is not expected to be an important fate process, because there is no chromophore for absorption of ultraviolet light (>290 nm) found in sunlight at tropospheric altitudes (Hubrich and Stuhl 1980; VanLaethem-Meuree et al. 1979). A laboratory experiment performed in sealed Pyrex ampules showed loss of 1,1,1-trichloroethane in 2 weeks under the influence of sunlight; however, catalysis by the Pyrex surface was probably responsible for the enhanced reactivity (Buchardt and Manscher 1978).

The relatively long tropospheric residence time for 1,1,1-trichloroethane suggests that migration to the stratosphere should be important. An estimated 11–15% of 1,1,1-trichloroethane released to the atmosphere is expected to survive and migrate to the stratosphere (Prinn et al. 1987; Singh et al. 1992). In the stratosphere, chlorine atoms produced from 1,1,1-trichloroethane by ultraviolet light may interact with ozone contributing to the destruction of the stratospheric ozone layer. Compared to CFC-11 (trichlorofluoromethane), the steady state ozone depletion potential of 1,1,1-trichloroethane has been estimated to be 0.1–0.16 (Gibbs et al. 1992; Solomon and Albritton 1992).

6.3.2.2 Water

Slow biodegradation of 1,1,1-trichloroethane can occur under both anaerobic and aerobic conditions. Anaerobic degradation of 1,1,1-trichloroethane is thought to occur predominantly through reductive dechlorination by methane-producing bacteria (Vargas and Ahlert 1987; Vogel and McCarty 1987) and by sulfate-reducing organisms (Cobb and Bouwer 1991; Klecka 1990). Determined experimental half-lives for anaerobic degradation using mixed culture bacteria ranged from 1 day to 16 weeks in the laboratory (Bouwer and McCarty 1983a, 1984; Hallen et al. 1986; Parsons et al. 1985; Vogel and McCarty 1987; Wood et al. 1985), based on a study from an injection well, after 3 months of injection, the predicted half-life of 1,1,1-trichloroethane in an aquifer was 200–300 days (Bouwer and McCarty 1984). Results obtained in a grab sample study of an aquifer suggest that anaerobic biodegradation of 1,1,1-trichloroethane will not occur (Wilson et al. 1983); however, the spiked concentration of 1,1,1-trichloroethane in the study, 1 mg/L, was in a range determined to be toxic to microorganisms (Barth and Bunch 1979; Benson and Hunter 1977; Vargas and Ahlert 1987). Another grab sample study, performed using more realistic concentrations, indicates that 1,1,1-trichloroethane slowly degrades under anaerobic conditions to 1,1-dichloroethane in groundwater (Parsons and Lage 1985; Parsons et al. 1985). However, when mixed anaerobic cultures were provided with acetate as primary substrate, the biodegradation of secondary substrate 1,1,1-trichloroethane occurred even without acclimation at concentrations exceeding

1 mg/L (Hughes and Parkin 1992). A laboratory study showed that anaerobic biodegradation of 1,1,1-trichloroethane did not occur under denitrification conditions even after 8 weeks of incubation (Bouwer and McCarty 1983b).

Aerobic biodegradation in surface water and groundwater is not likely to be an important fate process since experimental studies did not indicate significant aerobic degradation of 1,1,1-trichloroethane (Klecka et al. 1990; Mudder and Musterman 1982; Nielson et al. 1990; Wilson and Pogue 1987). One study showed that 1,1,1-trichloroethane underwent aerobic degradation in the presence of Fe^{+2}/porphyrin solution (82% in 21 days), thought to be a catalyzed reductive chlorination (Klecka and Gonsior 1984). It is difficult to interpret these results in terms of the potential for environmental significance. One study reported that 1,1,1-trichloroethane underwent moderate biodegradation with significant concomitant volatilization (Tabak et al. 1981); however, experimental details are not sufficient to rule out loss due solely to volatilization. Halogenated aliphatic hydrocarbons, including 1,1,1-trichloroethane, act as cometabolic substrates for certain aerobic chemotrophs. In such cases, the organisms grow on another substrate and the enzymes induced under the particular growth conditions fortuitously biodegrade the halogenated aliphatics (Leisinger 1992). Such aerobic biodegradation of 1,1,1-trichloroethane up to a concentration of 1.2 mg/L was observed with methane-oxidizing (methanotrophic) bacteria isolated from an aquifer (Arvin 1991).

Anaerobic biodegradation proceeds via reductive dechlorination (Leisinger 1992; McCarty 1993). The major product from the anaerobic degradation of 1,1,1-trichloroethane has been identified as 1,1-dichloroethane, which slowly degrades to chloroethane in a secondary reaction (Hallen et al. 1986; Vogel and McCarty 1987). Therefore, total biodegradation of 1,1,1-trichloroethane is feasible by combining anaerobic dehalogenation with subsequent aerobic treatment (Leisinger 1992). Aerobic biodegradation of 1,1,1-trichloroethane, on the other hand, proceeds via substitutive and oxidative mechanisms with the production of trichloroethyl alcohol, which is further oxidized to chloride, carbon dioxide, and water (McCarty 1993).

Products from the abiotic degradation of 1,1,1-trichloroethane have also been identified. Acetic acid can arise from the hydrolysis of 1,1,1-trichloroethane (calculated half-life of 1.2 years at 25 °C and pH 7). Elimination of HCl can produce 1,1-dichloroethene (Hallen et al. 1986; Parsons et al. 1985; Vogel and McCarty 1987). The calculated half-life for this reaction is 4.8 years at 25 °C and pH 7 (Ellenrieder and Reinhard 1988). The half-lives of abiotic degradation of 1,1,1-trichloroethane by reaction with

nucleophiles, such as HS^- and $S_2O_2^-$, which might be present in water, should be insignificant compared to the other processes described (Haag and Mill 1988). A 2.8 mmol aqueous solution of 1,1,1-trichloroethane reacted with ozone (concentration 1 mg/L) with a half-life of >32 days at 22 °C and a pH of 7 (Yao and Haag 1991). Therefore, reaction with ozone will not be an important process for the transformation of 1,1,1-trichloroethane present in natural bodies of water.

6.3.2.3 Sediment and Soil

Data are lacking on the degradation of 1,1,1-trichloroethane in soil. In a grab sample experiment, anaerobic degradation of 1,1,1-trichloroethane occurred slowly in soil (16% in 6 days) (Henson et al. 1988). If the microorganisms in the soil were first activated by using methane as a nutrient source, 46% of 1,1,1-trichloroethane degraded during the same period under aerobic conditions (Henson et al. 1988). Incubation of 1,1,1-trichloroethane in soil under aerobic conditions resulted in no measurable biodegradation (Klecka 1990).

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

The manufacture and use of 1,1,1-trichloroethane was scheduled to be phased out by 2002 under the Clean Air Act (EPA 2004m). Since it is no longer in use domestically, the levels estimated in the environment, other than near point sources, should drop to insignificant amounts.

6.4.1 Air

1,1,1-Trichloroethane has been identified in urban, rural, and indoor air throughout the United States at concentrations shown in Table 6-3. Due to the nature of 1,1,1-trichloroethane's use, volatilization to the atmosphere is a predictable outcome, and thus, its widespread detection is not unexpected. It is the only chlorinated ethane regularly seen as a background pollutant in the troposphere (Spence and Hanst 1978). For the year 1980, an estimated global atmospheric quantity of 1,1,1-trichloroethane, based on absolute concentrations obtained over a 3-year period, was 2.58×10^9 kg (5,690 million pounds) (Prinn et al. 1983). An estimated average concentration of 0.14 ppb in 1980, based on a characterization of its sources, abundance, and atmospheric sinks, was also reported (Ramanathan et al. 1985). The data indicate that the average atmospheric concentration of 1,1,1-trichloroethane was 0.13 ppb for the middle of 1988 (Khalil

Table 6-3. Detection of 1,1,1-Trichloroethane in Air

Media type/location	Sampling dates	Number of samples	Concentration (ppb)		Reference
			Range	Mean	
Urban air:					
El Monte, CA	1982–1983	NS	0.8–6.6[a]	2.1	Shikiya et al. 1984
Los Angeles, CA	1983		0.8–2.4	NS	
Dominguez Hills, CA			0.6–2	NS	
Riverside, CA			0–0.8	NS	
Research Triangle Park, NC	1980	61	0.0024–43.7[b]	0.83	Wallace et al. 1984a
Houston, TX	1980		0.134–1.499[c]	0.353	Singh et al. 1992
St. Louis, MO			0.132–0.896	0.235	
Denver, CO			0.171–2.699	0.713	
Riverside, CA			0.205–1.349	0.747	
Staten Island, NY	1981		0.221–1.427	0.468	
Pittsburgh, PA			0.158–1.595	0.486	
Chicago, IL			0.241–0.909	0.476	
Iberville Parish, LA	1977	11	ND–1.61[b]	0.31	Pellizzari 1982
Kib–Buc Disposal Site, NJ	1977	4	ND–22.0		
Rutherford, NJ	1978	150	ND–6.3	0.17	Bozzelli and Kebbekus 1979
Rutherford, NJ (North)		29	ND–3.6	0.55	
Rutherford, NJ (Clifton)		26	ND–trace		
Newark, NJ		110	ND–7.8	0.39	
Bridgewater, NJ		22	ND–0.83	0.05	
Los Angeles Basin	1972	59	0.01–2.30	0.37	Simmonds et al. 1974
Los Angeles, CA	1984	23	NS–3.70	0.74	Pellizzari et al. 1986
Los Angeles, CA	1979		0.224–5.144[c]	1.028	Singh et al. 1981
Phoenix, AZ			0.197–2.813	0.823	
Oakland, CA			0.142–0.967	0.290	
New Jersey					
fall (day)	1981	86	ND–86[b]	0.60[d]	Wallace et al. 1985, 1987a; Hartwell et al. 1984b
fall (night)		86[e]	ND–7.3	0.68	
summer	1982	60		0.93	
winter	1983	8		0.26	
Bozeman, MN	1976[e]	1	0.15		Taketomo and Grimsrud 1977
Seagirt, NJ	1974	NS	0.044–0.20	0.10	Lillian et al. 1975
New York, NY			0.10–1.6	0.61	
Sandy Hook, NJ			0.030–0.330	0.15	
Delaware City, DE			0.03–0.30	0.10	

Table 6-3. Detection of 1,1,1-Trichloroethane in Air

Media type/location	Sampling dates	Number of samples	Concentration (ppb)		Reference
			Range	Mean	
Baltimore, MD			0.044–0.21	0.12	
Wilmington, OH			0.030–0.35	0.097	
Bayonne, NJ	1973		0.075–14.4	1.59	
Greensboro, NC	1982	32		11.1[b]	Wallace et al. 1987a
Devils Lake, ND		24		0.009[b]	
La Jolla, CA	1974–1976	23	0.13–1.1	0.00037	Su and Goldberg 1976
California coast (marine air)	1974	5	0.14–0.30	0.00019	
Washington, DC	1974	1	0.5		
Los Angeles (Chinatown), CA	1974	1	3.4		
Santa Monica, CA	1974	1	1.3		
Orange County, CA	1974	3	0.37–0.68		
Chicago, IL	1974	2	0.37–0.68		
Greensboro, NC	1980	20	NS–9.81[b]	0.33	Hartwell et al. 1984a
Baton Rouge, LA	198	127	NS–13.5	0.11	Pellizzari et al. 1984a, 1986
Houston, TX	1981	11	NS–1.41	0.47	
Bayonne/Elizabeth, NJ	1980	165	0.133–131[b]		Wallace et al. 1984a
Bayonne/ELizabeth, NJ	1981	80–90	NS–87[b]	1.68	Wallace et al. 1985
Chicago, IL	1986–1990	103	NS	0.61[b]	
St. Louis, IL		83		0.72[b]	Sweet and Vermette 1992
Hawthorne, CA	1987–1990	NS	0.8–7.0 0.8–18.0	NS	Hisham and Grosjean 1991
Long Beach, CA			2.2–14.7 2.2–9.9		
Anaheim, CA			0.5–8.5 13.2–22.2		
Los Angeles, CA			2.7–6.3 8.3–14.0		
Burbank, CA			1.2–6.1 7.1–28.4		
Azusa, CA			3.2–17.1		
Claremont, CA			3.3–15.0		
Los Angeles, CA			1.7–6.5		
Ventura, CA			0.5–2.7		
West Los Angeles, CA			1.6–2.2		
Los Angeles, CA (UCLA)			0.5–0.9		
Malibu, CA			0.5–1.6		

Table 6-3. Detection of 1,1,1-Trichloroethane in Air

Media type/location	Sampling dates	Number of samples	Concentration (ppb)		Reference
			Range	Mean	
Northeast Los Angeles, CA			0.8–7.2		
Burbank, CA			0.5–5.7 0.13–1.17		
Los Angeles, CA	February 1984	24	NS	6.3[b]	Wallace et al. 1988
Los Angeles, CA	May 1984	23		1.1[b]	
Contra Costa, CA	June 1984	10		0.52[b]	
Hawthorne, CA	1987–1990	NS	NS		Hisham and Grosjean 1991
fall				12.9	
summer				3.4	
Long Beach, CA					
fall				6.3	
summer				8.5	
Anaheim, CA					
fall				16.9	
summer				3.0	
Los Angeles, CA					
fall				9.9	
summer				4.5	
Burbank, CA					
fall				18.5	
summer				3.1	
Washington, DC	1989	5	0.28–0.42[b]	0.35[b]	EPA 1990b
Los Angeles, CA (winter)	1987	51	NS	1.09[b,f]	Hartwell et al. 1992
Columbus, OH	June–July 1989	NS		0.72	Spicer et al. 1996
Baton Rouge LA	Sept 1996–Aug1997	NS	NS	0.124	Mohamed et al. 2002
Brownsville TX	Sept 1996–Aug1997	NS	NS	0.107	
Brattleboro VT	Sept 1996–Aug1997	NS	NS	0.097	
Burlington VT	Sept 1996–Aug1997	NS	NS	0.094	
Camden NJ	Sept 1996–Aug1997	NS	NS	0.13	
El Paso TX	Sept 1996–Aug1997	NS	NS	0.097	
Garyville LA	Sept 1996–Aug1997	NS	NS	0.116	

Table 6-3. Detection of 1,1,1-Trichloroethane in Air

Media type/location	Sampling dates	Number of samples	Concentration (ppb)		Reference
			Range	Mean	
Hahnville LA	Sept 1996–Aug1997	NS	NS	0.122	
Port Neches TX	Sept 1996–Aug1997	NS	NS	0.12	
Rutland VT	Sept 1996–Aug1997	NS	NS	0.098	
Underhill VT	Sept 1996–Aug1997	NS	NS	0.084	
Winooski VT	Sept 1996–Aug1997	NS	NS	0.101	
Rural air:					
Pullmam, WA	1974–1975	NS	NS	0.100[c]	Grimsrud and Rasmussen1975
Eastern WA	1976	389	0.090[c]–0.18	0.135	Cronn et al. 1983
Stanford Hills, CA	1975	75		0.0776[c]	Singh et al. 1977
Point Reyes, CA		300	NS	0.0903	
Pacific NW, USA	1975 1976 1977 1978 1979 1980			0.087[c] 0.098 0.107 0.117 0.135 0.156	Rasmussen et al. 1981
Antarctica	1975 1976 1977 1978 1979 1980			0.045 0.057 0.070 0.085 0.095 0.102	
Pt. Barrow, AL	1980–1982	NS	0.150–0.172[c]	0.152 (0.168)[g]	Khalil and Rasmussen 1983
Midland, MI	1975	7	0.0916–0.188[h]	0.104	Russell and Shadoff 1977
Old Love Canal, NY	1978	9	ND–0.989[h]		Barkley et al. 1980
White Face Mountains, NY	1974	NS	0.032–0.13	0.067	Lillian et al. 1975
Mt Hood, OR	1981–1982	7	0.104–0.179	0.156	Rasmussen et al. 1983
Beaverton, OR	1982	7	0.154–0.363	0.202	
Mt. Cuyamaca, CA	1975	1		0.41	Su and Goldberg 1976
Montgomery Pass, NE				10.34	
Lytton Lake, CA				10.07	
Champain, IL	1986–1990	23	NS	0.2[b]	Sweet and Vermette 1992

Table 6-3. Detection of 1,1,1-Trichloroethane in Air

Media type/location	Sampling dates	Number of samples	Concentration (ppb)		Reference
			Range	Mean	
Chattanooga, TN	1986–1987	30	0.18–9.6[b]	3.98[b]	Parkhurst et al. 1988
San Nicolas Island, CA	1987	NS	0.55–0.57	NS	Hisham and Grosjean 1991
Kanawha Valley, WV	NS[e]			353.6[b]	Cohen et al. 1989
Minnesota at 25 sites	1991–1998	3,648		0.28	Pratt et al. 2000
Indoor Air:					
Old Love Canal, NY					
	1978	9	ND–0.220[h]	14	Barkley et al. 1980
Bozeman, MN	NS[e]	8	0.12–0.73		Taketomo and Grimsrud 1977
Greensoro, NC	1980	20	NS–28.7[b]	1.15	Hartwell et al. 1984a; Pellizzari et al. 1986
Baton Rouge, LA	1981	27	NS–45.0	0.28	
Houston, TX	1981	11	NS–5.73.7		
Elizabeth/Bayonne, NJ	1981 1982 1983	25 71 9	NS–163[b] NS–22.2 NS–31.53.7	2.96 1.83	Pellizzari et al. 1986
Los Angeles, CA					
winter	1984	25	NS–37.0	4.44	
summer	1984	23	NS–17.4	1.46	
Antioch–W. Pittsburgh, CA					
Public access buildings	1984	16	NS–2.590.78		Wallace et al. 1987c
Recently constructed building after occupancy	1983–1985	70.55–7.5[b] 30.73–69.6	0.36–18.3		
Elderly home	NS	NS	0.12–22.6	NS	Pellizzari et al. 1984b
Los Angeles, CA	1987	51			Hartwell et al. 1992
kitchen			NS	1.78[b]	
living area			NS	2.33[b]	
Chattanooga, TN	1986				Parkhurst et al. 1988
residential		34	0.37–37[b]	5.1[b]	
public buildings		37	0.92–50[b]	13[b]	
Dallas, TX					Gallagher and Kurt 1990
incubator air in an intensive care nursery	1988		460,000–160,000[i]	95,000[i]	
Washington DC, U.S. EPA headquarters:					EPA 1990b
Waterside Mall		51	0.42–4.8[b]	1.6[b]	
Crystal City		5	0.56–0.70[b]	0.61[b]	

Table 6-3. Detection of 1,1,1-Trichloroethane in Air

Media type/location	Sampling dates	Number of samples	Concentration (ppb)		Reference
			Range	Mean	
Fairchild		5	1.2–1.3[b]	1.2[b]	
Neenah, WI, telephone switching office	1987				Shields and Weschler 1992
second floor break room		NS	NS	0.17[b]	
second floor break room		1	NS	0.11[b]	
		NS	NS	0.056[b]	
		1	NS	0.26[b]	
Southern California museums	1986				Hisham and Grosjean 1991
El Pueblo			1.2–5.1	NS	
LACMA			2.9–3.9	NS	
Page			>30	NS	
Getty			3.7–4.8	NS	
Southwest			2.2–7.3	NS	
Personal air:					
Chapel Hill, NC	1978		172.65–19.6[b]	15.0	Zweidinger et al. 1983
Beaumont, TX		11	1.51–196	33	Wallace et al. 1982
New Jersey	1981				Wallace et al. 1987a
fall (day)		346–48	ND–6,040[b]	3.5[d]	
New Jersey					Wallace et al. 1985
fall (night)		339–41	ND–1520	3.5	
fall (summer)	1982	148		1.7[d]	
winter	1983	48		4.0	
Bayonne/Elizabeth, NJ	1980	165 (9)	0.13–130[b]	1.7	Wallace et al. 1984a
Research Triangle Park, NC		61 (3)	0.024–43.2	0.82	
Bayonne/Elizabeth, NJ	1981	339–348	NS–61,100	22.2	Wallace et al. 1984b, 1985
Devils Lake, ND	1982	24	[b]	4.63[b]	Wallace et al. 1987a
Greensboro, NC	1982	32	[b]	5.92[b]	
Los Angeles, CA	February 1984	110	NS	17.8[b]	Wallace et al. 1988
Los Angeles, CA	May 1984	50	NS	8.1[b]	
Contra Costa, CA	June 1984	67	NS	2.9[b]	
Los Angeles, CA	1987	51	NS	2.6[b,f]	Hartwell et al. 1992
Near waste/landfill site:					
Hamilton, OH	1983	NS	0.36–23.8[b]	NS	Levine et al. 1985
Elizabeth, NJ	1980	NS	ND–330	NS	
New Jersey (NPLHS)	1983				

Table 6-3. Detection of 1,1,1-Trichloroethane in Air

Media type/location	Sampling dates	Number of samples	Concentration (ppb)		Reference
			Range	Mean	
Site A		24	ND–4.49	0.38	Laregina et al. 1986
Site B		15	ND–1.84	0.51	Harkov et al. 1985
Site C		14	ND–18.97	3.04	
Site D		14	ND–2.89	0.57	
Site E		15	ND–1.22	0.84	
Landfill LF		15	ND–7.15	1.29	
New Jersey	1976	4	ND–22.2	9.0	Pellizzari 1982
California	1984–1986	NS	ND–3,600[i]	NS	Wood and Porter 1987
Stanislaus County, CA	1987				Hodgson et al. 1992
on site		NS	<10–13,000	NS	
outside (nearby residential home)		NS	NS	0.3	
inside (nearby residential home [basement])		NS	NS	0.7	
20 Class II landfills:					
Long Island, NY	1982				Walsh et al. 1988
on site			140[i]		
nearby residential homes			1		
nearby school			1		
Troposphere					
Western Pacific Region 114–165 °E longitude latitudes > 25 °N					Blake et al. 1997
7-12.6 km	Sept–Oct 1991	175	0.108–0.166[c]	0.125[c]	
	Feb–Mar 1994	274	0.078–174[c]	0.119[c]	
2-7 km	Sept–Oct 1991	309	0.107–0.188[c]	0.126[c]	
	Feb–Mar 1994	347	0.111–0.377[c]	0.127[c]	
0-2 km	Sept–Oct 1991	149	0.695–0.114[c]	0.137[c]	
	Feb–Mar 1994	134	0.128–0.550[c]	0.133[c]	
Western Pacific Region 114–165 °E longitude latitudes < 25 °N					
7–12.6 km	Sept–Oct 1991	233	0.104–0.145[c]	0.124[c]	

Table 6-3. Detection of 1,1,1-Trichloroethane in Air

Media type/location	Sampling dates	Number of samples	Concentration (ppb)		Reference
			Range	Mean	
	Feb–Mar 1994	454	0.100–0.134[c]	0.122[c]	
2–7 km	Sept–Oct 1991	243	0.104–0.162[c]	0.122[c]	
	Feb–Mar 1994	341	0.111–0.133[c]	0.123[c]	
0–2 km	Sept–Oct 1991	172	0.102–0.194[c]	0.124[c]	
	Feb–Mar 1994	178	0.117–0.189[c]	0.127[c]	

[a]Monthly mean
[b]Data reported in µg/m^3; converted to ppb using the conversion factor 1 ppb=5.4 µg/m^3
[c]Data reported in ppt; converted to ppb using the conversion factor 1 ppb=1,000 ppt
[d]Weighted geometric mean
[e]Date of study not given
[f]Data reported as median
[g]Summer (winter)
[h]Data reported in ng/m^3; converted to ppb using the conversion factor 5,400 ng/m^3=1 ppb
[i]Data reported in ppm; converted to ppb using the conversion factor 0.001 ppm=1 ppb

ND = not detected; NS = not specified

and Rasmussen 1989). Based on absolute concentrations obtained over a 12-year period, a global atmospheric concentration of 157 ppt (0.157 ppb) was estimated for 1,1,1-trichloroethane in the middle of 1990 (Prinn et al. 1992). Atmospheric measurements at several surface stations made between 1978 and 1990 indicated that the global average concentration of 1,1,1-trichloroethane increased at a rate of 4.4±0.2% over this time period (Prinn et al. 1992).

The measured concentration of 1,1,1-trichloroethane in urban air usually ranges from 0.1 to 1 ppb; however, levels ≤1,000 ppb have been observed in large urban areas or near hazardous waste sites. Representative monitoring data on the concentration of 1,1,1-trichloroethane in air can be found in Table 6-3. Rural levels of 1,1,1-trichloroethane are typically <0.2 ppb. The long atmospheric lifetime of 1,1,1-trichloroethane allows the compound to be carried a considerable distance from its initial point of release; detectable levels have been measured in numerous remote areas throughout the world and are shown in Table 6-3 (Class and Ballschmiter 1986; DeBortoli et al. 1986; Guicherit and Schulting 1985; Hov et al. 1984; Ohta et al. 1976; Rasmussen et al. 1982). The mean background concentration of 1,1,1-trichloroethane over subarctic North America in the summer of 1990 was 0.155 ppb (Wofsy et al. 1994). During a period of arctic haze, the concentration of 1,1,1-trichloroethane in the polluted Arctic air was 2–15% higher than in clean air over the Arctic (Khalil and Rasmussen 1993). The mean concentration of 1,1,1-trichloroethane in the troposphere over northwestern Pacific region (114–165 °E longitude) was found to range from 0.12 to 0.13 ppb (Blake et al. 1997, Table 6-3 Mohamed et al. 2002). The concentrations of 1,1,1-trichloroethane near industrial facilities emitting 1,1,1-trichloroethane were found to be only marginally higher than those measured at sites away from facilities emitting 1,1,1-trichloroethane.

The concentration of 1,1,1-trichloroethane in indoor air is variable, and seems to depend on individual practices, season, outdoor concentration, age of building, and building air-exchange characteristics (Cohen et al. 1989; Hartwell et al. 1987a, 1987b, 1992; Hisham and Grosjean 1991; Lioy et al. 1991; Wallace 1986; Wallace et al. 1986a, 1986b, 1988, 1989, 1991). For example, college students monitored simultaneously on the same campus were found to have levels of personal exposure varying by as much as two orders of magnitude (Wallace et al. 1982; Zweidinger et al. 1983). Further, two studies suggest that buildings with air conditioning may have higher levels of 1,1,1-trichloroethane in indoor air (Cohen et al. 1989; Hisham and Grosjean 1991). 1,1,1-Trichloroethane has been found at levels ≤ 70 ppb in newly constructed buildings (Wallace et al. 1987b). The concentration of 1,1,1-trichloroethane in new and recently renovated buildings was as high as 290 ppb (Rothweiler et al. 1992). New carpet and other

new building materials that contain 1,1,1-trichloroethane may be responsible for higher levels in new and renovated buildings. During normal periods (no renovation or construction), the levels of total volatile organics are inversely proportional to the air exchange rate of the building (Shields and Weschler 1992). Higher levels of 1,1,1-trichloroethane are expected to be found in indoor air during winter than any other season (Wallace et al. 1991). The effect of outdoor air on indoor air was demonstrated by the detection of higher levels of 1,1,1-trichloroethane during outdoor stagnation conditions when the levels were higher compared to levels under non-stagnation conditions (Lioy et al. 1991). Representative data taken from five geographic areas located throughout the United States report indoor concentrations of 0.3–4.4 ppb and outdoor concentrations of 0.11–0.92 ppb (Pellizzari et al. 1986). Several studies have determined the presence of 1,1,1-trichloroethane in products expected to be in most households (Section 6.5) (EPA 1987; Maklan et al. 1987; Sack et al. 1992; Spicer et al. 1987). An EPA Region V (Minnesota, Wisconsin, Michigan, Illinois, Indiana, and Ohio) National Human Exposure Assessment Survey (NHEXAS) detected a mean concentration of 1,1,1-trichloroethane to be 1.15 ppb in indoor air samples collected from residential areas from July 1995 to May 1997 (Bonanno et al. 2001). The maximum concentration of trichloroethane detected in the same study was 34 ppb.

6.4.2 Water

1,1,1-Trichloroethane has been identified in surface water, groundwater, drinking water, effluent, rain, snow, and urban runoff. The amount of the chemical detected in surface and groundwater depends upon the location of the sampling point. Concentrations in surface water removed from point-source emissions such as industrial waste water, hazardous waste sites, and spill locations are usually <1 ppb. In random samples of groundwater taken in the United States, concentrations have ranged from 0 to 18 ppb. Groundwater samples obtained near sources of release to soil or the ground have been as high as 11,000 ppb. Drinking water from surface or groundwater sources contained 1,1,1-trichloroethane concentrations of 0.01–3.5 ppb.

Data on the occurrence of 1,1,1-trichloroethane in water are presented in Table 6-2. Data on the concentration of 1,1,1-trichloroethane in effluent can be found in Table 6-4.

1,1,1-Trichloroethane was found in groundwater at hazardous waste sites in 18.9% of 178 sites from the Comprehensive Emergency Response, Compensation and Liability Act (CERCLA) database, making it the seventh most frequently detected compound in this study (Plumb 1987). It was found in water

Table 6-4. Detection of 1,1,1-Trichloroethane in Effluent

Media type/location	Sampling dates	Number of samples	Concentration (ppb)		Reference
			Range	Mean	
Industrial waste water:					
Textile plants	1975	64	2–300[a]	NS	Rawlings and Deangelis 1979
Municipal waste water:					
Los Angeles, CA	1978	NS			
primary				340[a]	Young 1978
secondary				<10	Young et al. 1983
Los Angeles, CA					
primary				130	
secondary				180	
Orange County, CA					
primary				4,000	
secondary				<10	
San Diego, CA					
primary				68	
Water factory 21					McCarty and Reinhard 1980
influent	1976	50	<0.3–38[a]	4.794	
Orange County, CA	1978				
effluent		51	0.1–1.2	0.07	
influent		28	0.3–15	2.9	
effluent		17	<0.1–41	0.14	
Chicago, IL, Calumet plant	1980	2			Lue-Hing et al. 1981
influent				14[a]	
effluent				<10	
John Egan plant		1		11	
influent				<10	
effluent					
Denver, CO					
reuse influent	1985–1986	14	1.70–6.9[a]	3.74	Rogers et al. 1987
Landfill leachates:					
Collegeville, PA[b]	1983[c]	NS	1–60	NS	Varma 1985
Minnesota[d]	1983	6	ND–7.6[a]		Sabel and Clark 1984
Nuclear power plant emissions:					

Table 6-4. Detection of 1,1,1-Trichloroethane in Effluent

Media type/location	Sampling dates	Number of samples	Concentration (ppb)		Reference
			Range	Mean	
Denver, CO	1989				Sturges and Taylor 1990
downwind		6	0.06–0.623[e]	0.27[e]	
upwind		8	0.088–0.251[e]	0.137[e]	

[a]Data reported in µg/L; converted to ppb using the conversion factor 1 ppb=1 µg/L
[b]National Priority Hazardous Waste Site
[c]Date of study not given
[d]Municipal Solid Waste site
[e]Data reported in ppt; converted to ppb using the conversion factor 1 ppb=1,000 ppt

ND = not detected; NS = not specified

samples from 42 of 357 Contract Laboratory Program (CLP) sites; the concentration range of the mean values was 1.75–1,100 ppb (Viar 1987).

6.4.3 Sediment and Soil

Monitoring data on the occurrence of 1,1,1-trichloroethane in soil are not as extensive as for water or air, which precludes an estimate of typical levels found in soil. The reported levels of 1,1,1-trichloroethane in soils are shown in Table 6-5. In two grab soil samples taken in 1980 from two former sludge lagoons of a solvent recovery operation at Southington, Connecticut, the measured concentrations of 1,1,1-trichloroethane were 23,000 and 120,000 ppb (Hall 1984). The limited data on the concentration of 1,1,1-trichloroethane in soil may be due to its rapid volatilization from soil, its ability to leach through soil, or both. The concentrations of 1,1,1-trichloroethane in sediments are shown in Table 6-2. The mean concentration of 1,1,1-trichloroethane in sediments from a river passing through an industrial area in Japan was 0.4 ppb, although it was not detected in the river water or in the sediment of a river passing through a non-industrial area (Grotoh et al. 1992).

6.4.4 Other Environmental Media

Limited data on the occurrence of 1,1,1-trichloroethane in other media were located. 1,1,1-Trichloroethane has been found in raw, processed, and prepared food products. These data are presented in Table 6-6. 1,1,1-Trichloroethane has been found in fish and shrimp taken from the Pacific Ocean at average concentrations of 2.7 and <0.3 ppm, respectively (Young et al. 1983). It has also been detected in clams and oysters from Lake Pontchartrain, Louisiana, with mean concentrations ranging from 39 to 310 ppm (Ferrario et al. 1985) and from a polluted river in Japan at concentrations ranging from 0.6 to 1.8 ppb wet weight (wt/wt) (Grotoh et al. 1992). 1,1,1-Trichloroethane was detected in 2 of 265 table-ready foods of FDA Total Diet Study at an average concentration of 12.7 ppb (Heikes et al. 1995).

1,1,1-Trichloroethane has been detected in four shoe and leather glues in Denmark in the concentration range 0.1–2.7% (wt/wt) (Rastogi 1992). Six samples of glues manufactured in the United States and in Europe and used for assembling various consumer goods and toys contained 1,1,1-trichloroethane in the concentration range 0.002–97.5% (wt/wt) (Rastogi 1993). In various brands of imported typing correction fluids in Singapore, the equilibrium vapor phase concentration of 1,1,1-trichloroethane ranged from <1 to 95% (v/v) (Ong et al. 1993).

Table 6-5. Detection of 1,1,1-Trichloroethane in Soils

Media type/location	Sampling dates	Number of samples	Concentration (ppb)		Reference
			Range	Mean	
Urban:					
Southington, CT	1980	2	23,000–120,000[a]		Hall 1984
National Priorities List:					
Lang property, NJ	1985				EPA 1987c
surface		NS	ND–980[b]	322	
subsurface		NS	ND–140	71	
Gallaway Ponds site, TN	1984	NS	13,000[c]		EPA 1987b
1,1,1-Trichloroethane producer/user:					
Plant A	1976–1977	4	0.06–0.68		Battelle Labs 1977
Plant B		2	0.45–0.94		
Plant C		2	0.13–0.28		
Plant D		2	0.14–1.0		
User A		2	0.40–0.65		
Summit National, OH (NPL site)	1987				EPA 1988a
on-site surface		31	3[d]–51,000[b]	2,216[b]	
on-site subsurface (2–4 feet)		5	10–43,000[b]	8,391[b]	
on-site subsurface (4–6 feet)		2	5–2,800[d,b]	561[b]	
on-site subsurface (6–8 feet)		15	4[d]–230,000[b]	10,252[b]	
Residence near a landfill:					
Stanislaus County, CA	September 1987	NS	1.4–11	4.9	Hodgson et al. 1992
	October 1987		2.8–9.4	6.1	

[a]Data reported in µg/L; converted to ppb using the conversion factor 1 ppb=1 µg/L
[b]Data reported in µg/kg; converted to ppb using the conversion factor 1 ppb=1 µg/kg
[c]Data reported in ppm; converted to ppb using the conversion factor 1 ppb=0.001 ppm
[d]Data were estimated.

ND = not detected; NS = not specified

Table 6-6. Detection of 1,1,1-Trichloroethane in Foods

Type	Food	Sampling dates	Concentration (ppb)		Reference
			Range	Mean	
Unprepared, uncooked, off-the-shelf	Split peas	NS		3	Daft 1987
	Allspice			16,000	
	Pickling spice			549	
	Celery seed			909	
	Tea			10	
	Dumplings (dry)			7	
	Instant hot cereal			421	
	Ready-to-eat cereals			4	
	Cake mix (golden)			8	
	Cake mix (yellow)			87	
	Pancake mix			16	
	Breaded fish			2	
	Onion rings (precooked)			76	
Intermediate	Yellow corn meal	1984		3.8	Heikes and Hopper 1986
	Fudge brownie mix		2.9–3.0	0.74	
	Yellow cake mix				
Fresh	Nectarine	1985–1986		NS[a]	Takeoka et al. 1988
Cooked, aroma	Beef	NS		NS[a]	Galt and MacLeod 1984
Prepared	Bakers cheese	NS		1.3[b]	Uhler and Diachenko 1987
	Cottage cheese	NS	2.7–10.6	6.4	Miller and Uhler 1988
	Ricotta cheese		ND–30.6	3.0	
	Mozzarella (skim milk)		9.5–37.3	1.2	
	Vanilla ice cream		NS–7,500		
	Chocolate ice cream				
	Butter pecan ice cream				
	Butter				
Cooked, aroma	Baked potatoes	NS		ND	Coleman et al. 1981
Ice	Commercial machine	1975 (NS)		0.0039[c]	Su and Goldberg 1976
Cereals	Shredded wheat	NS		4[b]	Daft 1988
	Raisin bran			6	
	Granola, plain			22	
	Oat ring			6	
	Rolled oats, cooked			35	
	Farina, cooked			8	
	Corn grits, cooked			3	

Table 6-6. Detection of 1,1,1-Trichloroethane in Foods

Type	Food	Sampling dates	Concentration (ppb)		Reference
			Range	Mean	
Vegetables	Peas, cooked	NS		1[b]	Daft 1988
	Peas, canned			2	
	Corn, boiled			2	
	Onion rings, cooked			9	
	French fries, cooked			2	
	Mashed potatoes			6	
	Sweet potatoes, candied			3	
	Cream of potato soup			2	
	Catsup			2	
Baked goods	Cornbread	NS		3[b]	Daft 1988
	Biscuits, baking powder			2	
	Blueberry muffins			11	
	Saltine crackers			7	
	Corn chips			9	
	Pancakes			3	
	Potato chips			8	
	Macaroni and cheese			2	
	Chocolate cake/icing			40	
	Yellow cake			40	
	Coffeecake, frozen			14	
	Donuts, cake, plain			17	
	Sweet roll, Danish			29	
	Cookies, chocolate chip			8	
	Cookies, sandwich			28	
	Apple pie, frozen			14	
Nuts/nut products	Peanut butter, creamy	NS		10[b]	Daft 1988
	Peanuts, dry roasted			24	
	Pecans			228	
Dairy products	Whole milk	NS		1[b]	Daft 1988
	Chocolate milk			5	
	Milkshake, chocolate			152	
	Yogurt, strawberry			2	
	Cheese, processed			8	
	Cheese, cheddar			16	
	White sauce			10	
	Margarine, stick			13	
	Butter, stick			18	
	Cream, half & half			4	
	Ice cream, chocolate			4	
	Instant pudding, chocolate			1	

Table 6-6. Detection of 1,1,1-Trichloroethane in Foods

Type	Food	Sampling dates	Concentration (ppb)		Reference
			Range	Mean	
Dairy products *(continued)*	Ice cream sandwich			15	
	Ice milk, vanilla			520	
	Butter	Nov 20–27 1992	1.0–4	1.82	Miyahara et al. 1995
	Margarine		ND–74	5.29	
	Milk		ND		
	Ice cream		ND–3.2	0.88	
	Yogurt, plain		ND–1.2	0.06	
	Ice milk		ND–0.9	0.2	
Sugars, jams, candy	Candy, milk chocolate	NS		15[b]	Daft 1988
Meats, meat dishes	Beef, ground, fried	NS		8[b]	Daft 1988
	Beef, chuck roast			6	
	Beef, sirloin, cooked			10	
	Pork, ham, cured			5	
	Pork chop, cooked			76	
	Pork, sausage, cooked			7	
	Pork, bacon, cooked			2	
	Pork roast, loin, cooked			3	
	Lamb chop, cooked			7	
	Veal cutlet, cooked			8	
	Chicken, pieced, fried			14	
	Frankfurters, cooked			33	
	Bologna			8[b]	
	Salami			8	
	Tuna, canned in oil			3	
	Shrimp, breaded, fried			3	
	Fish sticks, cooked			12	
	Pizza, cheese, cooked			8	
	One-fourth pound hamburger			27	
	Meatloaf, beef			15	
	Chicken noodle casserole			4	
	Lasagna			2	
	Potpie, chicken			6	
	Frozen dinner, chicken			10	
	Brown gravy			2	
Infant/toddler blends	Oatmeal, applesauce, banana	NS		6[b]	Daft 1988

Table 6-6. Detection of 1,1,1-Trichloroethane in Foods

Type	Food	Sampling dates	Concentration (ppb)		Reference
			Range	Mean	
Fruits	Apple, red, raw	NS		3[b]	Daft 1988
	Grapes, purple/green			2	
	Raisins, dried			16	
	Prunes, dried			21	
	Avocado, raw			32	
	Grapefruit juice			4	
	Lemonade			11	
Clear beverages	Grape juice	NS		3[b]	Daft 1988
	Whiskey, 80 proof			2	

[a]Detected in sample; no quantitative results given
[b]Data reported in ng/g; converted to ppb using the conversion factor 1 ppb=1 ng/g
[c]Data reported in pg/mL; converted to ppb using the conversion factor 1 ppb=1,000 pg/mL

ND = not detected; NS = not specified

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Although the manufacture and use of 1,1,1-trichloroethane was scheduled to be phased out by 2002 under amendments made to Section 604 of the Clean Air Act (EPA 2004m); it is still being manufactured in the United States by two producers with production volumes of at least 100 million pounds as of 2002 (EPA 2002; SRI 2003). Its relatively long atmospheric half-life and continued production suggest that the general population may be expected to have continued exposure to this compound into the foreseeable future.

The ubiquitous occurrence, in the past, of low levels of 1,1,1-trichloroethane in ambient air and other environmental samples, together with the fact that many consumer products previously used to contain this chemical, suggests that much of the general population of the United States was exposed to low levels of 1,1,1-trichloroethane. This exposure could have occurred occupationally, environmentally, or as a result of the use of commercial products that contain 1,1,1-trichloroethane. 1,1,1-Trichloroethane has been detected in the blood, milk, breath, and urine of humans. An EPA Region V (Minnesota, Wisconsin, Michigan, Illinois, Indiana, and Ohio) National Human Exposure Assessment Survey (NHEXAS) detected a mean concentration of 1,1,1-trichloroethane to be 0.05 ppb in blood samples collected from July 1995 to May 1997 (Bonanno et al. 2001). The maximum concentration of trichloroethane detected in the same study was 2.7 ppb. Data on human body burdens associated with this compound can be found in Table 6-7. Table 5-2 provides a sampling of consumer products containing 1,1,1-trichloroethane. The levels of this chemical in human breath have been correlated with its levels in personal air by probability-based population studies (Wallace et al. 1985, 1986c, 1987a, 1988).

If the average urban concentration of 1,1,1-trichloroethane is taken to be 1 ppb and the average rural concentration is taken to be 0.1 ppb, then daily non-occupational intakes of 108 and 10.8 µg/day, respectively, can be obtained based on an average human air intake of 20 m^3/day. In areas where 1,000 ppb have been measured, the daily intake using this methodology would be 108 mg. However, Wallace et al. (1984a) have determined that the mean daily air exposure for 12 subjects from urban New Jersey and Research Triangle Park, North Carolina, was 370 mg. Further, the mean daily intake from all sources (air, food, and water) was between 50 and 1,000 mg/day for 1,1,1-trichloroethane (Wallace et al. 1984a).

Table 6-7. Detection of 1,1,1-Trichloroethane in Human Samples

Media type/location	Sampling dates	Number of samples	Concentration (ppb)		Reference
			Range	Mean	
Adipose tissue:					
United States	1984	46	ND–830[a]	48	Stanley 1986a, 1986b
Blood/serum:					
New Orleans		250	ND–26	NS	Antoine et al. 1986
Old Love Canal	1978	9	0.24–1.8[b]		Barkley et al. 1980
Denver	1976	3	1,300–2,700[c]	1,800	Gunter et al. 1977
U.S. NHANES III Non-smokers	NS	126	ND–0.0106[d]	0.0035	Ashley et al. 1995
U.S. NHANES III Smokers	NS	42	ND–0.0132[d]	0.0052	
U.S. NHANES III Non-occupationally exposed	NS	574	NS	0.34	Ashley et al. 1994
Milk:					
Bridgeville, PA; Bayonne, NJ; Jersey City, NJ; Baton Rouge, LA		12	NS		Pellizzari et al. 1982
Breath:					
Chicago, IL		387		0.0018[d]	Krotosznski et al. 1979
Texas		10	ND–140 (µg/hour)	40	Conkle et al. 1975
Old Love Canal, NY	1978	9	Trace–0.513[e]		Barkley et al. 1980
Chapel Hill, NC	1978	17	1.1–8.72[f]	81.81	Zweidinger et al. 1983
Beaumont, TX		17	0.081–29.6	15.97	
New Jersey					
fall	1981	322		1.2[f]	Wallace et al. 1987a
summer	1982	110		0.95	
winter	1983	49		0.37	
Devils Lake, ND	1980	23		1.7	Wallace et al. 1984a
		48(9)	0.022–16.0[f]	0.88	
Bayonne/Elizabeth, NJ	1981	295–339	ND–95	0.88[g]	Wallace et al. 1985
		17(3)	0.053–1.4	0.11	
Los Angeles, CA	1984				Wallace et al. 1987d
winter		112–115		1.17[g,f]	
spring		51		0.70	
Antioch-Pittsburgh, PA		66–69		0.017	Wallace et al. 1984b, 1985, 1986b, 1987a
Elizabeth-Bayonne, NJ	1981	295–339	NS–96.2	2.78	

Table 6-7. Detection of 1,1,1-Trichloroethane in Human Samples

Media type/location	Sampling dates	Number of samples	Concentration (ppb)		Reference
			Range	Mean	
Elizabeth-Bayonne, NJ	1981	48	0.022–15.7		Wallace et al. 1984a
Research Triangle Park, NC	1981	17	0.054–1.142		
Urine:					
Old Love Canal, NY	1978	9	0.03–0.180	100	Barkley et al. 1980

[a]Data in ng/g; 1 ppb=1 ng/g
[b]Data in ng/mL; 1 ppb=1 ng/mL
[c]Data in mg/dL; 1 ppb=0.00001 mg/dL
[d]Data in ng/L; 1 ppb=1000 ng/L
[e]Data in ng/m^3; 1 ppb=5400 ng/m^3
[f]Data in µg/m^3; 1 ppb=5.4 µg/m^3
[g]Weighted geometric mean

ND = not detected; NHANES = National Health and Nutrition Examination Survey; NS = not specified

1,1,1-Trichloroethane has been detected in newly constructed buildings (Wallace et al. 1987b). 1,1,1-Trichloroethane was found in 216 of 1,159 common household products preselected to contain solvents at concentrations >0.1% by weight (Sack et al. 1992). In a similar study, 1,1,1-trichloroethane was found in all 67 categories of household products (1,026 brands tested) likely to be in the average U.S. home (EPA 1987; Maklan et al. 1987). The categories of these common household products are given in Table 5-2. The occurrence of 1,1,1-trichloroethane in 62% of the effluent samples taken from a community septic tank also suggests the presence of this compound in household products (De Walle et al. 1985).

Human exposure could occur directly via ingestion of contaminated water, but also indirectly through the inhalation of 1,1,1-trichloroethane that has volatilized from contaminated tap water. Based on a theoretical concentration of 1 mg/L (ppm) of 1,1,1-trichloroethane in tap water, the average estimated air concentrations for the entire house, bathroom, and shower stall were $2.3x10^{-4}$, $5.1x10^{-3}$, and $2.6x10^{-2}$ mg/L, respectively (McKone 1987). For a tap water concentration of 20 mg/L, the estimated daily exposure to 1,1,1-trichloroethane was 20.0 mg from ingestion and 22.8 mg from inhalation while showering (Foster and Chrostowski 1986). The Total Exposure Assessment Methodology (TEAM) studies demonstrated that levels of personal air exposure determined using samples obtained on the same day could vary by orders of magnitude for subjects living in the same municipality, most likely as a result of variances in consumer practices and occupation (Hartwell et al. 1987a, 1987b, 1992; Wallace 1986, 1987; Wallace et al. 1986a, 1986b, 1988, 1989; Zweidinger et al. 1983). The maximum exposure levels of 1,1,1-trichloroethane during personal activities were: 185 ppb when visiting the dry cleaners, 18.5 ppb when working in a chemistry lab, 12 ppb when working as a lab technician, 48 ppb when using household cleaners, 20 ppb when using pesticides, and 20 ppb when using paint (Wallace et al. 1989). Exposure of the general population from the use of commercial products may be more significant than exposure resulting from industrial release.

According to the National Occupational Exposure Survey (NOES) conducted by NIOSH between 1981 and 1983, it has been statistically estimated that ≈2,528,300 workers in the United States were potentially exposed to 1,1,1-trichloroethane (NIOSH 1990). The largest number of workers are exposed in the following types of industries/services: sewing machine operators in apparel industry; registered nurses, maids, janitors and cleaners in hospitals; electricians, technicians, assemblers, installers, machinists and repairers in electrical and electronic industry; and janitors and cleaners in building maintenance service. From the existing monitoring data, it appears that most occupational exposure occurs by inhalation.

Specific industrial applications of 1,1,1-trichloroethane that might result in elevated levels of exposure are processes involving the degreasing and cleaning of fabricated metal parts (Gunter et al. 1977; Kominsky 1976; Levy and Meyer 1977; Markel 1977), manufacture of electronic components (Giles and Philbin 1976), mixing and application of commercial resins (Giles 1976), and spray painting and spray gluing (Whitehead et al. 1984). Table 6-8 lists occupations in which 1,1,1-trichloroethane has been detected in the air. Other occupations where workers can be exposed to 1,1,1-trichloroethane include automotive assembly plants (Nelson et al. 1993), kraft pulp mills (Rosenberg et al. 1991), and fuel cell assembly plants (NIOSH 1993). In a survey (1990–1991) of a fuel cell assembly plant, the levels of 1,1,1-trichloroethane in some of the personal breathing zone and general area samples were found to exceed the NIOSH short-term exposure limit of 350 ppm (NIOSH 1993). More current worker information was not available; however, since the production and use of 1,1,1-trichloroethane is being phased out, exposures would be expected to decrease. Exposure to 1,1,1-trichloroethane should be limited to those workers who are still involved in the manufacture and production of this compound or the limited uses as allowed for essential applications in the medical industry and aviation industry or the export of 1,1,1-trichloroethane as specified under Section 604 of the Clean Air Act.

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).

Table 6-8. Occupational Air Levels of 1,1,1-Trichloroethane

Location/occupation	Sampling dates	Concentration (ppb)		Reference
		Range	Mean	
Bozeman, MT	1976			
Auto repair garage			2.2	Taketomo and Grimsrud 1977
Bookstore			6.7	
Restaurant			0.2	
Department store		0.8–1.7		
Newspaper press room			2.2	
Grocery store		1.9–21		
Dry cleaner		1.8–14.4		
Chemistry building (academic)		0.1–1.2		
Tampa, FL				
Telephone central office	1979	27–65		Oblas et al. 1979, 1980
Hobbs, NM				
Telephone business office			50	
Waltham, MA				
Laboratory air			4.5	
Organic solvent recycling plant	1984	ND–20,000[a]	3,110	Kupferschmid and Perkins 1986
Booth spray painting/gluing	1981	NS–22,000[a]	1,200	Whitehead et al. 1984
Screw machine manufacturing company, AR	1976	12,000–99,800[b]		Markel 1977
Rifle scope producer, Denver, CO	1976	7,700–478,000[b]		Gunter et al. 1977
Heating and cooling coil manufacturing, IL	1976	1,460–16,600[b]		Levy and Meyer 1977
Electric apparatus manufacturing, PA	1975	2,500–79,500[a]		Giles 1976
Electrical resistor manufacturing, PA	1976	6,000–83,000[a]		Giles and Philbin 1976
Valve part manufacturer, IN	1976	4,000–37,000[a]		Kominsky 1976
Aircraft manufacturer, GA	1983–1984	ND–23,000[a]		Salisbury et al. 1986
Sport racket manufacturer, CO	1985	NS		Pryor 1987
Nail manufacturer, CO	1987	7,510–406,000[b]		NIOSH 1987
Fiber manufacturer, IL	1986	59–115[b]		Daniels et al. 1988
Mens' shirt company, IN	1974			Nord 1974
Film optical shops, NY	1979	500–1,320,000[b]		Peter and Edelbrock 1980
Joint/shaft manufacturer, IN	1979	800–1,300[a]		McQuilkin et al. 1979
Battery manufacturer, CO	1979	9,160–36,400[b]		NIOSH 1980a

Table 6-8. Occupational Air Levels of 1,1,1-Trichloroethane

Location/occupation	Sampling dates	Concentration (ppb)		Reference
		Range	Mean	
Typesetter/photographer, GA	1979	3,900–4,600[a]		NIOSH 1980b
Graphic services, OH	1979	<1,000[a]		NIOSH 1980c
Welding shop	1979	3,200–4,799[a]		Vegella 1979
Suitcase manufacturer, CO	1978	500–756,000[a]		Apol and Singal 1979
Ski/tennis racquet manufacturing, CO	1979	22,500–85,800[b]		Gunter 1979
Sewer workers, OH	1981	1,000–40,000[a]		McGlothlin and Cone 1983
Solar cell producer, CA	1979	ND–74,000[b]		Briggs and Garrison 1982
Medical therapeutic system manufacturing, CO	1979	400–3,600[a]		NIOSH 1980d
Navigation information products, CO	1981	549–2,750[b]		Gunter 1983
Tractor manufacturer, ND	1979	ND–62,600[a]		NIOSH 1980e
U.S. Department of the Treasury, DC	1982	NS		Lee 1984
School district print shop, OR	1983	100[a]		Apol and Helgerson 1983
Electrical maintenance company, OH	1981	123,000–385,000[b]		Kominsky and Lipscomb 1985
Electrical commutators manufacturers, IL	1983	ND–4[a]		Almaguer 1985
Crystal fabricator, CO	1984	366–2700[b]		Gunter and Thoburn 1986
Silk screening of textiles, KS	1975	ND–75,000[b]		Hervin 1975
Aluminum vane manufacturers, OH	1976	74,000–396,000[a]		Giles 1977
Catapult cylinder manufacturers, OH	1975	2,400–18,400[a]		Giles 1977
Chemical recovery plant, OH	1980	1,900–4,500[b]		Albrecht 1980
Pump manufacturer, NY	1978–1979	ND–2,930		Fannick 1980
Uranium company, WY	1980	ND–155,000[b]		Gunter 1980
Theater, NY	1985	458–10,700[b]		Fannick 1986

[a]Data reported in ppt; converted to ppb using the conversion factor 1 ppb=1,000 ppt
[b]Data reported in mg/m^3; converted to ppb using the conversion factor 1 ppb=0.0054 mg/m^3

ND = not detected; NS = not specified

Exposures of the embryo or fetus to volatile organic compounds such as 1,1,1-trichloroethane may occur if the expectant mother is exposed. A newborn infant may be exposed by breathing contaminated air and through ingestion of mother's milk that can contain small amounts of 1,1,1-trichloroethane. Children may be exposed through accidental ingestion of products containing 1,1,1-trichloroethane. Older children and adolescents may be exposed to 1,1,1-trichloroethane in their jobs or hobbies, or through deliberate solvent abuse by "sniffing." Epidemiological studies and case reports discussing reproductive and/or developmental toxicity of 1,1,1-trichloroethane in humans have been reviewed in Chapter 3.

Young children often play close to the ground and frequently play in dirt, which increases their dermal exposure to toxicants in dust and soil. They also tend to ingest soil, either intentionally through pica or unintentionally through hand-to-mouth activity. Children, thus, may be orally and dermally exposed to 1,1,1-trichloroethane present as a contaminant in soil and dust. 1,1,1-Trichloroethane has a log organic carbon-water partition coefficient of 2.03, indicating low adsorption to soil (Chiou et al. 1979; Friesel et al. 1984). Most of the 1,1,1-trichloroethane present in the upper layers of the soil is volatilized to air within 24 hours (vapor pressure =124 mm Hg at 25 °C, Boublik et al. 1984). The rapid volatilization of 1,1,1-trichloroethane results in inhalation being the most likely route of exposure.

Children breathe in more air per kilogram of body weight than an adult. Therefore, a child in the same micro-environment as an adult is likely to be exposed to more 1,1,1-trichloroethane from ambient air. Young children are closer to the ground or floor because of their height. The 1,1,1-trichloroethane vapors being heavier than air (vapor density =4.63 g/mL; HSDB 2004) tend to concentrate near the ground. The children, therefore, are at a greater risk of exposure than adults during accidental spills of 1,1,1-trichloroethane.

Children may also be exposed to fumes of 1,1,1-trichloroethane by working with or playing near sources. Children's exposure also occurs through accidental ingestion and inhalation of the chemicals into the lungs. Children are also exposed to higher concentrations of 1,1,1-trichloroethane (0.1–1 ppb, Table 6-3) in urban areas compared to children living in rural areas (concentrations typically <0.2 ppb, Table 6-3).

Animal studies demonstrated that, once absorbed, 1,1,1-trichloroethane is distributed by the blood to tissues and organs throughout the body, including developing fetuses, with preferential distribution to fatty tissues (Holmberg et al. 1977; Katagiri et al. 1997; Schumann et al. 1982a; Takahara 1986b).

There are no existing studies that have monitored the level of exposure from 1,1,1-trichloroethane to children. Most uses of 1,1,1-trichloroethane are associated with occupational purposes, so it is unlikely that children will receive significant doses. Under extreme conditions where products containing high concentrations of 1,1,1-trichloroethane are used in the presence of children in an enclosed area with little or no ventilation, children could receive significant exposure. There are studies that examine the exposure to children from parents' work clothes, skin, hair, tools, or other objects removed from the workplace (NIOSH 1995); however, this type of "take home" or secondary exposure is unlikely due to the high volatility of 1,1,1-trichloroethane. Additional exposure from consumer products can occur, but is unlikely to be significant, although little data are available at this time.

It is not known whether children differ in their weight-adjusted intake of 1,1,1-trichloroethane. However, children drink more fluids per kg of body weight than adults (NRC 1993) and 1,1,1-trichloroethane has been detected in drinking water (Section 6.4.2, Table 6-2).

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

The general population is potentially exposed to low levels of 1,1,1-trichloroethane through the ingestion of contaminated water or food and by breathing air contaminated with this compound. Since most applications and uses of 1,1,1-trichloroethane have been or are currently being discontinued, human exposure is expected to decrease accordingly. The manufacture and use of 1,1,1-trichloroethane was scheduled to be phased out by 2002 under the Clean Air Act (EPA 2004m). Since it is no longer in use, the exposure of the general population should drop to insignificant levels. Low levels of contamination in drinking water sources have been documented (Althoff et al. 1981; Barkley et al. 1980; Burmaster 1982; EPA 1986a; Krill and Sonzogni 1986; Wallace et al. 1984a; Zaki 1986). According to Table 6-2, levels of 0.01–12,220 ppb 1,1,1-trichloroethane have been found in drinking water sources. 1,1,1-Trichloroethane was used as a component of adhesives for food packaging, and this practice may have contributed to human exposure by ingestion (Miller and Uhler 1988). Airtight, highly-insulated houses are likely to have high indoor concentrations from use of household products containing 1,1,1-trichloroethane. Very high levels of exposure are expected to occur for those who intentionally inhale 1,1,1-trichloroethane for its euphoric/narcotic properties.

Workers who are still involved in processes using this compound may encounter high exposure levels. Occupations in which 1,1,1-trichloroethane has been found in the air are given in Table 6-8; however, it is

noted that many of these occupational exposures are no longer expected to occur today since the production and use of 1,1,1-trichloroethane is being phased out. Analysis of these data shows that ambient air concentrations in industries using 1,1,1-trichloroethane are up to 4 orders of magnitude higher than what is typically found in urban air.

1,1,1-Trichloroethane was used in some adhesive remover pads of incubators in intensive care nurseries, and there is evidence that infants in incubators could be exposed to high concentrations of 1,1,1-trichloroethane (Gallagher and Kurt 1990). This use of 1,1,1-trichloroethane has been discontinued.

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 1,1,1-trichloroethane 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 1,1,1-trichloroethane.

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 1,1,1-trichloroethane are well documented, and little additional information in this area is required. Only one BCF for 1,1,1-trichloroethane was located in the available literature. This value is, however, consistent with what would be expected based on the other physical and chemical properties of 1,1,1-trichloroethane.

Production, Import/Export, Use, Release, and Disposal. Historical data on the production, use, release, and disposal of 1,1,1-trichloroethane in the United States are well represented in the literature. The past production volumes of 1,1,1-trichloroethane manufactured in the United States is known. According to the 1990 amendments to the Clean Air Act and the Montreal Protocol, future U.S. production was to be cut incrementally until a total phase-out by January 1, 2002 (EPA 2004m). However, current data suggests that large quantities of 1,1,1-trichloroethane are still being produced domestically, and information regarding the current production volumes as well as export volumes are important to assess the potential for exposure. The past use of 1,1,1-trichloroethane is well-documented. It was used extensively in industrial applications, and it was found in numerous consumer products for the home. Mandates on production, however, are expected to decrease the use of 1,1,1-trichloroethane and subsequent potential exposure to 1,1,1-trichloroethane.

There are a few food monitoring studies in the literature that provide several examples of food contamination with 1,1,1-trichloroethane. The ubiquitous nature of 1,1,1-trichloroethane suggests that additional information in this area would allow a complete determination of the levels of human exposure to this chlorinated solvent. The release of 1,1,1-trichloroethane to the environment is well established since there are numerous studies that indicate the presence of this compound in environmental media. The quantity of 1,1,1-trichloroethane released to the environment during its production, formulation, and use is known. 1,1,1-Trichloroethane is listed on the Toxics Release Inventory (TRI). Methods for the disposal of 1,1,1-trichloroethane exist. Data on the removal of 1,1,1-trichloroethane from waste streams during biological treatment processes are lacking. Information on the amount of 1,1,1-trichloroethane disposed of annually is scarce. Rules and regulations governing the disposal of 1,1,1-trichloroethane exist.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. TRI, which contains this information for 2001, became available in 2002. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

Environmental Fate. Data on the environmental fate of 1,1,1-trichloroethane are well represented in the literature. The partitioning of 1,1,1-trichloroethane from soil or water to the atmosphere is well established, and there is sufficient evidence to indicate that the compound can leach into groundwater. The relatively slow rate of degradation and the major routes of 1,1,1-trichloroethane degradation in all

environmental compartments have been established. The relatively long persistence of 1,1,1- trichloroethane in the atmosphere indicates that a significant portion of this compound migrates to the stratosphere. Data on the biodegradation of 1,1,1-trichloroethane in soil are particularly lacking.

Bioavailability from Environmental Media. Numerous toxicokinetic and toxicity studies in humans and animals have demonstrated the bioavailability of 1,1,1-trichloroethane from air and drinking water. Although some data on the bioavailability of 1,1,1-trichloroethane from air to mammalian skin (Mattie et al. 1994), and from air to other mammalian tissues (blood, muscle, liver) (Connell et al. 1993) are available, no studies on the bioavailability of 1,1,1-trichloroethane from food or soil were located. Some of the important routes of exposure to 1,1,1-trichloroethane for residents near waste sites will be inhalation of airborne dusts, ingestion of soil (children) and dermal contact with contaminated soil (mostly children). Therefore, it would be helpful to develop reliable data for the bioavailability of 1,1,1-trichloroethane from dust as a result of inhalation of contaminated airborne dust, from soil as a result of ingestion of soil, and from soil as a result of dermal contact with soil.

Food Chain Bioaccumulation. 1,1,1-Trichloroethane is not believed to bioconcentrate in fish and aquatic organisms; thus, it is not expected to biomagnify in the food chain. There are limited data regarding food chain biomagnification of 1,1,1-trichloroethane.

Exposure Levels in Environmental Media. Volumes of data exist on levels of 1,1,1-trichloroethane in environmental media, with the exception of levels in soil samples. Continued monitoring of environmental media is warranted. Blind monitoring at this stage, however, might be replaced with methods that allow both the continued determination of the environmental burden of 1,1,1-trichloroethane and correlation with human burden, like that performed in the TEAM studies. These and other studies have estimated human intake of 1,1,1-trichloroethane from environmental media. For members of the general population near hazardous waste sites, total exposure to 1,1,1-trichloroethane will include exposure from environmental media and exposure from consumer products.

Reliable monitoring data for the levels of 1,1,1-trichloroethane in contaminated media at hazardous waste sites are needed so that the information obtained on levels of 1,1,1-trichloroethane in the environment can be used in combination with the body tissue/fluid levels of 1,1,1-trichloroethane to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. 1,1,1-Trichloroethane has been detected in human tissues and expired air. Studies have recently determined that the potential for exposure of the general population may be significantly higher inside the home. Additional information that correlates the lifestyle of the individual with the total body burden of 1,1,1-trichloroethane would aid in reducing future exposure to the general population. This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. A study on usefulness of intervention methods in cases of inhalant abuse by pregnant women would be helpful. More research is needed to rule out concomitant risk factors and to identify specific chemicals and patterns of use associated with adverse effects.

Children are at a greater risk of inhalation exposure to 1,1,1-trichloroethane as they breathe in more air per kilogram of body weight than an adult. They also spend more time closer to ground because of their height. 1,1,1-Trichloroethane vapors, being heavier than air, tend to concentrate closer to the ground, thereby increasing the risk for children. No data are available on the exposure of the children to 1,1,1-trichloroethane present in the air.

Means of protecting young children from ingestion of home products containing 1,1,1-trichloroethane need study and action. Child-proof containers and clearer warnings to parents should be considered to avoid unwanted exposure.

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 1,1,1-trichloroethane were located. This substance is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for subregistries 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

The Federal Research in Progress (FEDRIP 2004) database provides additional information obtainable from a few ongoing studies that may fill in some of the data needs identified in Section 6.8.1.

Researchers at Physical Optics Corporation (POC) proposes to develop a group-specific active optical chemical sensor for halohydrocarbons (including trichloroethylene, dichloroethylene, perchloroethylene, and 1,1,1-trichloroethane) that can be interfaced with a cone penetrometer for subsurface applications. No liquid chemical substances will be used in the final sensor design, enabling simple fiber optic-based downhole deployment.

Researchers at University of Washington, College of Forest Resources propose to test the ability of several plant strains to take up and transform various chlorinated hydrocarbons, including carbontetrachloride, chloroform, bischloromethane, 1,1,1-trichloroethane, perchloroethylenes, trichloroethylene, dichloromethanes, and vinyl chloride using laboratory mass balance reactors. They will identify the mechanisms involved in the chlorinated hydrocarbon oxidation in poplar and use molecular methods to enhance that activity.

7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring 1,1,1-trichloroethane, its metabolites, and other biomarkers of exposure and effect to 1,1,1-trichloroethane. 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

In the analysis of 1,1,1-trichloroethane in biological materials, a key factor in the determination is the sample matrix under consideration. In the broadest sense, this can be broken down into liquid samples (e.g., blood or urine), solid samples (which would include adipose tissue, liver samples), and expired air samples. After 1,1,1-trichloroethane has been recovered from the sample matrix, a number of similar techniques can then be used to complete the analysis. A synopsis of these methods can be found in Table 7-1. In general, the methods for determining the metabolites of 1,1,1-trichloroethane are the same as those used for the parent compound, with slight modifications (Nolan et al. 1984).

The quantification of 1,1,1-trichloroethane in blood and urine samples can be achieved by the initial use of purge and trap methodology (Antoine et al. 1986; Barkley et al. 1980). This technique involves the liberation of the volatile chlorinated hydrocarbon by bubbling an inert gas through the sample matrices at elevated temperatures (≈50–95 °C). Higher temperature increases the vapor pressure of the compound, and the bubbling action serves, essentially, to increase the gas-liquid partition, and thus volatilize the compound of interest. The gaseous sample is collected on an adsorption tube, which frequently uses a polymeric sorbent such as Tenax GC.

Table 7-1. Analytical Methods for Determining 1,1,1-Trichloroethane in Biological Samples

Sample matrix	Preparation method	Analytical method	Limit	Percent recovery	Reference
Exhaled air	Collection in Tedlar bag; adsorption on Tenax GC; thermal desorption	HRGC/MS	0.1 µg/m^3	87–94	Barkley et al. 1980; Wallace et al. 1984a, 1985, 1987a
Exhaled air	Collection in charcoal cloth wafers; desorption in carbon disulfide	GC/FID	2 mg/m^3 (for 50 L sample)	89–120	Glaser and Arnold 1989
Exhaled air	Collection into canister by portable spirometer; aliquot injection into a cryogenic trap	HRGC/MS	3.3 µg/m^3 (for 300 L sample)	94–98	Raymer et al. 1990
Urine	Purging at 50 °C; trapping on Tenax GC; thermal desorption into GC	HRGC/MS	No data	No data	Barkley et al. 1980
Adipose tissue	Purging at 95 °C; trapping on Tenax GC; thermally desorption at 250 °C	HRGC/MS	0.01 mg/kg	No data	Stanley 1986a,1986b
Blood	Purging at 50 °C; trapping on Tenax GC; thermal desorption	HRGC/MS	No data	No data	Antoine et al. 1986; Barkley et al. 1980
Blood	Purging at 30 °C; trapping on Tenax GC; thermal desorption into GC	HRGC/MS	0.049 µg/L	147	Ashley et al. 1992
Blood	Static headspace	HRGC/FID	<0.1 mg/L	214 (at 0.5 mg/L)	Dills et al. 1991
Liver, kidney, brain, heart, lung, perirenal fat and skeletal muscle	Homogenization with ice-cold saline and iso-octane; vortexing and centrifugation; iso-octane layer withdrawn for head space analysis	GC/ECD	1 ng	85.5–91.3	Chen et al. 1993
Milk	Purging at 70°C; trapping in Tenax GC; thermal desorption	HRGC/MS	No data	No data	Pellizzari et al. 1982

ECD = electron capture detector; FID = flame ionization detector; GC = gas chromatography; HRGC = high resolution gas chromatography; MS = mass spectrometry

At this point, the sample is analyzed by gas chromatography (GC), the analytical method of choice for volatile halogenated hydrocarbons. Information on the analysis of these samples by GC is presented in Section 7.2, with a discussion of the advantages and disadvantages of each method. The technique of Antoine et al. (1986) showed a 5% variance on a series of 2 ppb spiked samples, and the analysis had a linear response ranging from 0.5 to 50 ppb. Although infra-red spectrometry has less sensitivity than electron capture detectors (ECD), Hall electroconductivity detectors (HECD), and mass spectrometric detectors (MS), it has been used to quantify the levels of 1,1,1-trichloroethane in biological samples (IARC 1979).

The concentration of 1,1,1-trichloroethane in solid samples can be determined by headspace techniques, which involve analysis of the air above a heated sample in either a dynamic or a static system. In a static system, an aliquot of the atmosphere above the sample is obtained and analyzed by direct GC. In a dynamic system, an inert gas is passed over the top of a heated, rapidly stirred suspension of sample in water (Stanley 1986a, 1986b). The gas stream is then passed through an adsorption tube, trapping the volatile compounds. For adipose tissue, the detection limits were 0.01 mg/kg and the average recovery for spiked samples (concentration range 0.15–0.44 µg/20 g tissue) was 105%, with a precision of 11.8% (Stanley 1986a, 1986b).

In biological samples, losses during the sample preparation stage (weighing, transferring, etc.) can arise due to the volatility of 1,1,1-trichloroethane or from an incomplete recovery from the biological matrix. Samples should be analyzed shortly after they are obtained. Otherwise, they should be carefully stored at low temperature, preferably in a dessicator. Handling and manipulation also should be kept to a minimum, preventing both premature loss by volatilization and contamination of the sample through the adsorption of vapors from ambient air. The need for blank water with very low levels of volatile organic compounds (VOCs) has increased because of the constant improvement in the sensitivity of detection of these VOCs. A method that uses distillation in conjunction with helium stripping has been described to obtain high purity blank water (Cardinali et al. 1994).

7.2 ENVIRONMENTAL SAMPLES

A short description of the methods used for analysis of 1,1,1-trichloroethane in environmental samples is presented in Table 7-2. An extensive list of methods for analysis of 1,1,1-trichloroethane in

Table 7-2. Analytical Methods for Determining 1,1,1-Trichloroethane in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample Detection Limit	Percent recovery	Reference
Air	Charcoal tube collection and carbon disulfide desorption	GC/FID (NIOSH 1003)	18 ppm	No data	NIOSH 1987
Ambient air	Trapping on adsorbent; thermal desorption	HRGC/ECD	0.006 µg/m^3 (based on 127 L sample)	100	Frank and Frank 1988
Waste water	Purge and trap onto adsorbent; desorption into GC column by rapid heating	GC/HECD (EPA 601)	0.03 µg/L	75±12	EPA 1982c
Waste water	Purge and trap onto adsorbent; thermal desorption	GC/MS (EPA 624)	3.8 µg/L	102±16	EPA 1982a
Solid waste matrices, groundwater, liquid wastes, sediment	Purge and trap into adsorbent; thermal desorption	GC/MS (EPA-8240 SW 846)	5 µg/L (groundwater) 5 µg/kg (soil and sediment)	113 (at 10 µg/kg)	EPA 1986e
Soil	Purge and trap onto adsorbent; rapid heating desorption	GC/MS (EPA Contract Lab)	5 µg/kg	No data	EPA 1987a
Drinking water	Purge and trap onto adsorbent; backflush to cryogenically cooled trap	GC/HECD (EPA 502.1) HRGC/ HECD (EPA 502.2)	0.003 µg/L 0.01 µg/L	93±8 96±2.6	EPA 1986a
Drinking water, raw source water	Purge and trap onto adsorbent; backflush to packed or cryogenically cooled capillary trap	GC/MS (EPA 524.1) HRGC/MS (EPA 524.2)	0.3 µg/L 0.04 µg/L	105±8.9 100±4	EPA 1988b, 1988c
Food	Heating sample in closed container at 95 C for 55 minutes; analysis of headspace gas	GC/ECD	0.6–2.4 µg/kg (for various foods)	No data	Norman 1991

ECD = electron capture detector; EPA = Environmental Protection Agency; FID = flame ionization detector; GC = gas chromatography; HECD = Hall Electroconductivity detector; HRGC = high resolution gas chromatography; MS = mass spectrometry; NIOSH = National Institute for Occupational Safety and Health

environmental samples can be compiled from the literature. Two methods are commonly used for collection of 1,1,1-trichloroethane and other volatile organics in ambient and occupational air. One method uses adsorbents to trap and concentrate organics in air, and the other method uses passive stainless steel canisters (SUMMA canisters). The advantage of SUMMA canisters is that sample breakthrough does not occur with this method as it may occur with adsorbent tubes (Hsu et al. 1991). The disadvantages of the canister method are its inability to concentrate pollutants during sample collection and the potential analytical problems associated with the presence of moisture in the sample (Bianchi and Varney 1993). In all methods, however, there is a consensus that after the sample collection and preparation stage, mixture separation and quantitative analysis is best done with GC, coupled with an assortment of detectors. Standardized methods, with slight alterations, also can be used for determining the metabolites of 1,1,1-trichloroethane (Hallen et al. 1986; Parsons et al. 1985; Vogel and McCarty 1987).

The analysis of 1,1,1-trichloroethane in occupational air samples can be accomplished by NIOSH method 1003 (NIOSH 1987). The sample is obtained in the field with a pumping system to pass a measurable quantity of air (≈3 L) through a tube loaded with a solid sorbent, such as charcoal. Extraction of the tube with the solvent CS_2 liberates the 1,1,1-trichloroethane collected, an internal standard is added, and quantitation is then achieved by GC. For packed column analysis, an OV-101 column using a flame ionization detector (FID) is given as the preferred choice (alternates, including capillary columns, are acceptable). For the estimation of low levels of 1,1,1-trichloroethane in ambient air, thermal desorption following collection of the sample in an absorbent trap is the method of choice (Frank and Frank 1988).

Capillary columns are used to separate 1,1,1-trichloroethane from the other components in a mixture. Capillary columns provide wider versatility offering superior resolution of components. A comparison of capillary and packed column for analysis of volatile organics by GC is available (Clark and Zalikowski 1990). Narrow-bore capillary columns have high resolving power, but may not be suitable for headspace analysis because of easy column saturation (Ohno and Aoyama 1991). Wide-bore capillary columns are suitable in such cases (Ohno and Aoyama 1991). Different detectors can be used; ECD, HECD, and MS have been described. The MS is the most selective detector, but the HECD is the most sensitive. Both closed path and open path Fourier transform infrared spectrometry (FTIR) have recently been used for the determination of 1,1,1-trichloroethane in air (Carter et al. 1992; Trocha and Samimi 1993; Xiao and Levine 1993). Although the FTIR methods have higher detection limits than the some of the other

conventional methods, they afford the opportunity of remote monitoring of real-time samples (Xiao and Levine 1993).

In the analysis of 1,1,1-trichloroethane in air, the weakest link in analysis is irreversible adsorption of the desired compound to the sorbent material during sample collection. For highly volatile, nonpolar compounds such as 1,1,1-trichloroethane, complete removal of the substrate may not occur if the adsorbent irreversibly adsorbs the substrate.

The collection methods commonly used for water and aqueous effluents are grab or proportional sampling. However, a solid phase microextraction method, which involves exposing a fused silica fiber coated with a stationary phase to the aqueous sample until equilibrium is achieved, has been proposed as a collection method (Arthur et al. 1992). Analysis for 1,1,1-trichloroethane in municipal and industrial waste water is described in EPA method 601—purgeable halocarbons (EPA 1982a). A 5 mL grab sample is connected to an apparatus called a purging chamber. This chamber allows for an inert gas to be sparged through the water sample, carrying the 1,1,1-trichloroethane onto an adsorbent tube. The organics are subsequently desorbed from the adsorbent tube by rapid heating and back flushing into the GC column. Analysis is then made by GC elution using an HECD. Detection limits for this method are given as 0.03 µg/L, with a 75% average recovery for spiked samples. EPA test method 624, purgeables, also can be used for the analysis of 1,1,1-trichloroethane in waste water (EPA 1982a). This method is similar to method 601, except that MS is used for quantitation.

EPA method 502.1 can be used in the analysis of 1,1,1-trichloroethane in finished or raw source water (EPA 1986a). This method is analogous to method 601. The detection limit for this method is 0.003 µg/L, with an average recovery of 93%.

The EPA guidelines for contract laboratories (EPA 1986c) include methodology for the analysis of groundwater and soil samples. The method for water analysis is similar to method 524.1. Detection limits for this method are given at 5 µg/kg.

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 1,1,1-trichloroethane 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 1,1,1-trichloroethane.

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.

Exposure. The urinary concentration of 1,1,1-trichloroethane can be used as an appropriate biological indicator of exposure (Imbriani et al. 1988; Salkinoja-Salonen and Jokela 1991). Both in the experimentally exposed subjects and in the occupationally exposed workers, the urinary concentration of 1,1,1-trichloroethane showed a linear relationship to the corresponding environmental time-weighted average concentration with a correlation coefficient of 0.90–0.95 (Imbriani et al. 1988). Additional studies to determine 1,1,1-trichloroethane in urine are not required.

Effect. There is no known effect of 1,1,1-trichloroethane that can be quantitatively related to its exposure.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Analytical methodology for determining the levels of 1,1,1-trichloroethane and its biotic/abiotic degradation products such as 1,1-dichloroethene, 1,1-dichloroethane, and chloroethane in environmental samples are well established (Hallen et al. 1986; Mehran et al. 1988a; Parsons et al. 1985; Vogel and McCarty 1987). Existing methods that provide acceptable detection limits for background levels in the environment and for levels at which health effects occur can be found for all types of environmental samples. The precision, accuracy, reliability, and specificity of each method are well documented, and potential pitfalls have been described. Development of a new methodology to

determine 1,1,1-trichloroethane in environmental samples that would provide both increased speed and decreased levels of difficulty may be desirable in situations where environmental monitoring of 1,1,1-trichloroethane is required on a rapid or routine basis.

7.3.2 Ongoing Studies

No ongoing studies involving analytical techniques of 1,1,1-trichloroethane were found in a search of the Federal Research in Progress database (FEDRIP 2004).

8. REGULATIONS AND ADVISORIES

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

ATSDR has derived an MRL of 2 ppm for acute-duration inhalation exposure (14 days or less) to 1,1,1-trichloroethane, based on a LOAEL of 175 ppm for reduced performance of psychomotor tests in human volunteers in a study by Mackay et al. (1987).

ATSDR has derived an MRL of 0.7 ppm for intermediate-duration inhalation exposure to 1,1,1-trichloroethane based on a study by Rosengren et al. (1985), which found evidence of astrogliosis (increased glial fibrillary acid protein levels) in the brains of gerbils exposed to 210 or 1,000 ppm, but not 70 ppm, of 1,1,1-trichloroethane continuously for 3 months.

ATSDR has derived an MRL of 20 mg/kg/day for intermediate-duration oral exposure to 1,1,1-trichloroethane based on a NOAEL of 1,770 mg/kg/day for body weight effects in male mice administered 1,1,1-trichloroethane in the daily diet for 13 weeks (NTP 2000).

The EPA does not list a reference concentration or a reference dose for 1,1,1-trichloroethane on the Integrated Risk Information System (IRIS 2004). The EPA has classified 1,1,1-trichloroethane as group D, not classifiable as to human carcinogenicity, based on no reported human data and inadequate animal data (IRIS 2004).

Table 8-1. Regulations and Guidelines Applicable to 1,1,1-Trichloroethane

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	Group 3[a]	IARC 1999
WHO	Provisional guideline value for drinking water	2,000 µg/L	WHO 1996
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)	350 ppm	ACGIH 2003
	STEL	450 ppm	
	Carcinogenicity classification	A4[b]	
EPA	Class I controlled substance for the protection of stratospheric ozone	Yes	EPA 2004a 40CFR82, Subpart A, Appendix A
	Hazardous air pollutant		EPA 2004f 42USC7412
NIOSH	REL (15-minute ceiling TWA)	350 ppm	NIOSH 2004
	IDLH	700 ppm	
OSHA	PEL (8-hour TWA) for general industry	350 ppm	OSHA 2004c 29CFR1910.1000, Table Z-1
	PEL (8-hour TWA) for construction industry	350 ppm	OSHA 2004a 29CFR1926.55, Appendix A
	PEL (8-hour TWA) for shipyard industry	350 ppm	OSHA 2004b 29CFR1915.1000, Table Z
b. Water			
EPA	Drinking water standard	0.2 ppm	EPA 2004b 40CFR141.32
	Drinking water standards and health advisories		EPA 2004l
	1-Day HA for a 10-kg child	100 mg/L	
	10-Day HA for a 10-kg child	40 mg/L	
	DWEL	1 mg/L	
	Lifetime HA (70-kg adult)	0.2 mg/L	
	MCL	0.2 mg/L	EPA 2004c 40CFR141.61
	MCLG	0.2 mg/L	EPA 2004d 40CFR141.50
FDA	Bottled water	0.005 mg/L	FDA 2003a 21CFR165.110

Table 8-1. Regulations and Guidelines Applicable to 1,1,1-Trichloroethane

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
c. Food			
EPA	Exempt from the requirement of a tolerance for residues when used in the postharvest fumigation of citrus fruits		EPA 2004e 40CFR180.1012
	Exempt from the requirement of a tolerance for residues when used in accordance with good agricultural practices when applied to growing crops or to raw agricultural commodities after harvest		EPA 2004g 40CFR180.910
	Exempt from the requirement of a tolerance for residues when used in accordance with good agricultural practices in pesticide formulations applied to animals		EPA 2004h 40CFR180.930
FDA	Indirect food additive for use only as a component of adhesives		FDA 2003b 21CFR175.105
d. Other			
EPA	Community right-to-know; release reporting; effective date	01/01/1987	EPA 2004i 40CFR372.65
	Designated as a hazardous substance pursuant to Section 307(a) of the Clean Water Act, Section 112 of the Clean Air Act, and Section 3001 of RCRA		EPA 2004j 40CFR302.4
	Reportable quantity	1,000 pounds	
	Health and safety data reporting		EPA 2004k 40CFR716.120
	Effective date	10/04/1982	
	Sunset date	10/04/1992	
	Carcinogenicity classification	Group D[c]	IRIS 2004
	RfC	No data	
	RfD	Withdrawn	
STATE			
a. Air			
No data			
b. Water			
	Drinking water guidelines and standards		
Arizona		200 µg/L	HSDB 2004
Connecticut		200 µg/L	
Maine		200 µg/L	
Minnesota		600 µg/L	
New Jersey		30 µg/L	
c. Food			
No data			

Table 8-1. Regulations and Guidelines Applicable to 1,1,1-Trichloroethane

Agency	Description	Information	Reference
STATE *(cont.)*			
d. Other			
No data			

[a]Group 3: Not classifiable as to its carcinogenicity to humans.
[b]A4: Not classifiable as a human carcinogen.
[c]Group D: Not classifiable as to human carcinogenicity.

ACGIH = American Conference of Governmental Industrial Hygienists; CFR = Code of Federal Regulations; DWEL = drinking water equivalent level; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; HA = health advisory; HSDB = Hazardous Substances Data Bank; 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; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; RCRA = Resource Conservation and Recovery Act; REL = recommended exposure limit; RfC = reference concentration; RfD = reference dose; STEL = short-term exposure limit; TLV = threshold limit values; TWA = time-weighted average; USC = United States Codes; WHO = World Health Organization

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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 BMD10 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.

q1*—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) (TD50)—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.

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.

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, 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, 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: 1,1,1-Trichloroethane
CAS Number: 71-55-6
Date: September 3, 2004
Profile Status: Final Pre-Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 35
Species: Human

Minimal Risk Level: 2 [ ] mg/kg/day [X] ppm

Reference: Mackay CJ, Campbell L, Samuel AM, et al. 1987. Behavioral changes during exposure to 1,1,1-trichloroethane: Time-course and relationship to blood solvent levels. Am J Ind Med 11:223-240.

Experimental design: Twelve male volunteers participated in the experiment. Exposures were to 0, 175, or 350 ppm of 1,1,1-trichloroethane for 3.5 hours. Each volunteer was exposed to all three exposure concentrations in a balanced design, with a minimum of 2 weeks between exposures for any one individual. Test performance was assessed immediately before entering the exposure chamber and 20, 60, 120, and 180 minutes after entry. Tests were conducted for three psychomotor tasks (simple reaction time, choice reaction time, and tracking ability) and two cognitive tasks (syntactic reasoning and concentration). Volunteers also completed a stress-arousal checklist as part of the test battery. Blood levels of 1,1,1-trichloroethane were measured after 0, 20, 60, 120, and 180 minutes of exposure. Statistical analysis of variance to determine the main effects of exposure and duration was performed for the various tests, but pairwise statistical comparisons were not made.

Effects noted in study and corresponding doses: The tests for simple reaction time, choice reaction time and tracking ability all showed impaired psychomotor performance in volunteers exposed to 1,1,1-trichloroethane concentrations of 175 and 350 ppm. Effects were detected as soon as 20 minutes after the start of exposure at both concentrations. The test for simple reaction time appeared to be the most sensitive, exhibiting a 10-15% increase over baseline values. Observed performance changes correlated with 1,1,1-trichloroethane absolute blood levels. Performance in the cognitive tasks was not adversely affected by exposure, and neither was the self-reported mood of the volunteers. None of the subjects complained of headache, discomfort, or nausea.

Dose and end point used for MRL derivation: 175 ppm; decreased performance in psychomotor tests.

[ ] NOAEL [X] LOAEL

Although the LOAEL of 175 ppm in the critical study of Mackay et al. (1987) was associated with only a 3.5-hour exposure period, the acute-duration inhalation MRL is intended to be protective of a continuous acute-duration exposure. Data reported by Nolan et al. (1984) and Mackay et al. (1987) indicate that blood levels of 1,1,1-trichloroethane approach steady state during 2 hours of continuous inhalation exposure in humans. Neurobehavioral performance was correlated with 1,1,1-trichloroethane blood levels and there was little additional change in most measures of neurobehavioral performance as exposure duration increased from 2 to 3 hours (Mackay et al. 1987). Therefore, the LOAEL of 175 ppm was not adjusted for exposure duration.

Uncertainty Factors used in MRL derivation:

[X] 10 for use of a LOAEL
[ ] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? No

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose:

Other additional studies or pertinent information which lend support to this MRL: Gamberale and Hultengren (1973) observed psychophysiological test performance deficits in human subjects exposed to 250, 350, 450, and 550 ppm of 1,1,1-trichloroethane in consecutive 30-minute periods. All tasks tested were affected, including simple reaction time, choice reaction time, and tests for manual dexterity and perceptual speed. Statistically significant deficits were found as early as exposure period #2, during which the exposure concentration was 350 ppm. Muttray et al. (1999, 2000) found EEG changes consistent with increased drowsiness and slight irritant nasal responses in volunteers exposed to 200 ppm. In contrast, no psychomotor effects were seen in human volunteers exposed to 1,1,1-trichloroethane vapors at concentrations of 400-450 ppm for 4 hours once or twice in a 24-hour period (Salvini et al. 1971; Savolainen et al. 1981). Laine et al. (1996) found no consistent, statistically significant effects on electroencephalogram, visual evoked potential, or equilibrium in a group of 9 healthy male volunteers exposed to a constant 200 ppm of 1,1,1-trichloroethane vapors for 3 hours, followed by a 40-minute lunch break and a 40-minute afternoon exposure. A conservative approach was followed in the selection of Mackay et al. (1987) as the critical study for derivation of an acute-duration inhalation MRL because it identified the lowest LOAEL for psychomotor effects in humans following acute-duration inhalation exposure to 1,1,1-trichloroethane and was supported by results of Gamberale and Hultengren (1973) and Muttray et al. (1999, 2000). The choice of critical effect (neurological changes) is supported by animal studies, although exposure levels eliciting neurobehavioral and neurophysiological effects were much higher than those eliciting psychomotor effects in humans. For example, increased motor activity was observed in mice exposed to 1,250 ppm of 1,1,1-trichloroethane for 30 minutes (Bowen and Balster 1996). A 4-hour exposure of mice to 2,064 ppm resulted in impaired swimming behavior (DeCeaurriz et al. 1983). Albee et al. (1990b) reported 1,1,1-trichloroethane-induced alterations in flash evoked potential, somatosensory evoked potential, and electroencephalogram in rats exposed to 1,000 ppm for 6 hours per day on 4 consecutive days.

Agency Contact (Chemical Manager): Alfred F. Dorsey, D.V.M.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,1,1-Trichloroethane
CAS Number: 71-55-6
Date: September 3, 2004
Profile Status: Final Pre-Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 122
Species: Gerbil

Minimal Risk Level: 0.7 [ ] mg/kg/day [X] ppm

Reference: Rosengren LE, Aurell A, Kjellstrand P, et al. 1985. Astrogliosis in the cerebral cortex of gerbils after long-term exposure to 1,1,1-trichloroethane. Scand J Work Environ Health 11:447-456.

Experimental design: Groups of Mongolian gerbils (four/sex) were exposed to 70, 210, or 1,000 ppm of 1,1,1-trichloroethane vapor (cleaning grade, containing 5% dioxane-free stabilizers) continuously for 3 months. Each exposure group was paired with a control group consisting of eight sex-matched littermates of the test group. At the end of the exposure period, all animals were held for 4 months prior to sacrifice. Upon sacrifice, brains were weighed and prepared for analyses for the astroglial proteins S-100 and glial fibrillary acid (GFA) protein, both of which are biomarkers for astrogliosis.

Effects noted in study and corresponding doses: Levels of GFA protein in the sensorimotor cerebral cortex were significantly increased in gerbils exposed to 210 or 1,000 ppm of 1,1,1-trichloroethane, but not those exposed to 70 ppm. Levels of S-100 were not affected by treatment. Total protein levels were also unaffected by treatment. Brain weight was significantly reduced in gerbils exposed to 1,000 ppm.

Dose and end point used for MRL derivation: 70 ppm; biochemical changes (increased GFA protein) in the brain indicative of neuronal damage.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? No

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose:

NOAEL = 70 ppm

For a continuous exposure study, $NOAEL_{ADJ}$ = NOAEL:

$NOAEL_{ADJ}$ = 70 ppm

For a gas:extra respiratory effect, $NOAEL_{HEC} = NOAEL_{ADJ} \times L_A/L_H$, where L_A/L_H is the ratio of blood/gas partition coefficients in animals and humans. A blood/gas partition coefficient is not available for 1,1,1-trichloroethane in gerbils so the default value of $L_A/L_H = 1$ is used:

$NOAEL_{HEC} = 70 \text{ ppm} \times 1 = 70 \text{ ppm}$

The final MRL was calculated to be 0.7 ppm by dividing the concentration of 70 ppm by the uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Intermediate-duration inhalation MRL = 70 ÷ 100 = 0.7 ppm

Other additional studies or pertinent information which lend support to this MRL: The choice of neurological effects as the critical end point of 1,1,1-trichloroethane toxicity is supported by both human and animal studies, which identified the nervous system as a particularly sensitive target of 1,1,1-trichloroethane toxicity following short-term exposures. For example, Gamberale and Hultengren (1973) observed psychophysiological test performance deficits in human subjects exposed to 250, 350, 450, and 550 ppm of 1,1,1-trichloroethane in consecutive 30-minute periods. Mackay et al. (1987) reported psychomotor deficits in human subjects exposed to 175 or 350 ppm of 1,1,1-trichloroethane for 3.5 hours. Increased motor activity was observed in mice exposed to 1,250 ppm of 1,1,1-trichloroethane for 30 minutes (Bowen and Balster 1996). A 4-hour exposure of mice to 2,064 ppm resulted in impaired swimming behavior (DeCeaurriz et al. 1983). Albee et al. (1990b) reported 1,1,1-trichloroethane-induced alterations in flash evoked potential, somatosensory evoked potential, and electroencephalogram in rats exposed to 1,000 ppm for 6 hours/day on 4 consecutive days. Mattsson et al. (1993) noted decreased forelimb grip strength in rats exposed to 2,000 ppm of 1,1,1-trichloroethane, 6 hours/day, 5 days/week for 13 weeks.

Agency Contact (Chemical Manager): Alfred F. Dorsey, D.V.M.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,1,1-Trichloroethane
CAS Number: 71-55-6
Date: September 3, 2004
Profile Status: Final Pre-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 23
Species: Mouse

Minimal Risk Level: 20 [X] mg/kg/day [ ] ppm

Reference: NTP. 2000. Technical report on the toxicity studies of 1,1,1-trichloroethane (CAS No. 76-55-6) administered in microcapsules in feed to F344/N rats and B6C3F1 mice. National Toxicology Program. (41) NIH 004402.

Experimental design: Groups of male and female B6C3F1 mice (10 per group) were administered microencapsulated 1,1,1-trichloroethane in the diet at concentrations of 0, 5,000, 10,000, 20,000, 40,000, or 80,000 ppm, 7 days/week for 13 weeks. Untreated control groups of 10 males and 10 females were included in the study. Average doses of 1,1,1-trichloroethane calculated by the researchers 850, 1,770, 3,500, 7,370, and 15,000 mg/kg/day in male mice; and 1,340, 2,820, 5,600, 11,125, and 22,900 mg/kg/day in female mice, respectively. Clinical signs and body weights were recorded weekly. Food consumption was determined every 3–4 days. Vaginal cytology and sperm motility evaluations were performed on all mice in the vehicle control and the three highest dose groups of mice. At necropsy, all mice were subjected to gross pathological examinations, and the heart, lungs, thymus, liver, right kidney, and right testis were weighed. Mice in untreated and vehicle control and high-dose groups were subjected to complete histopathologic examinations.

Effects noted in study and corresponding doses: There were no exposure-related deaths. Food consumption was slightly greater in 1,1,1-trichloroethane-treated groups, relative to untreated and vehicle controls. However, the final mean body weights of all groups of 1,1,1-trichloroethane-treated male mice were significantly lower (9, 9, 12, 10, and 15% lower in the 5,000-, 10,000-, 20,000-, 40,000-, and 80,000-ppm male groups, respectively) than that of the untreated controls. Mean body weight gain in all treatment groups was also significantly less than that of the untreated controls (12, 16, 23, 22, and 33% lower in 5,000-, 10,000-, 20,000-, 40,000-, and 80,000-ppm groups, respectively). There were no indications of treatment-related clinical or histopathological effects. According to ATSDR policy, a treatment-related weight loss or a decrease in body weight gain of 10–19% (relative to controls) may be considered to represent a less serious adverse effect.

Dose and end point used for MRL derivation: 1,770 mg/kg/day was a NOAEL for reduced terminal body weight in male mice.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? No, the study authors provided the calculated doses.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose:

Other additional studies or pertinent information which lend support to this MRL: Decreased body weight appears to be a sensitive effect in other subchronic and chronic studies by oral or inhalation routes of exposure, either in the absence of other signs of toxicity (Adams et al. 1950; Bruckner et al. 2001; Prendergast et al. 1967) or at doses causing minimal liver lesions (Calhoun et al. 1981; Quast et al. 1978, 1988).

Agency Contact (Chemical Manager): Alfred F. Dorsey, D.V.M.

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

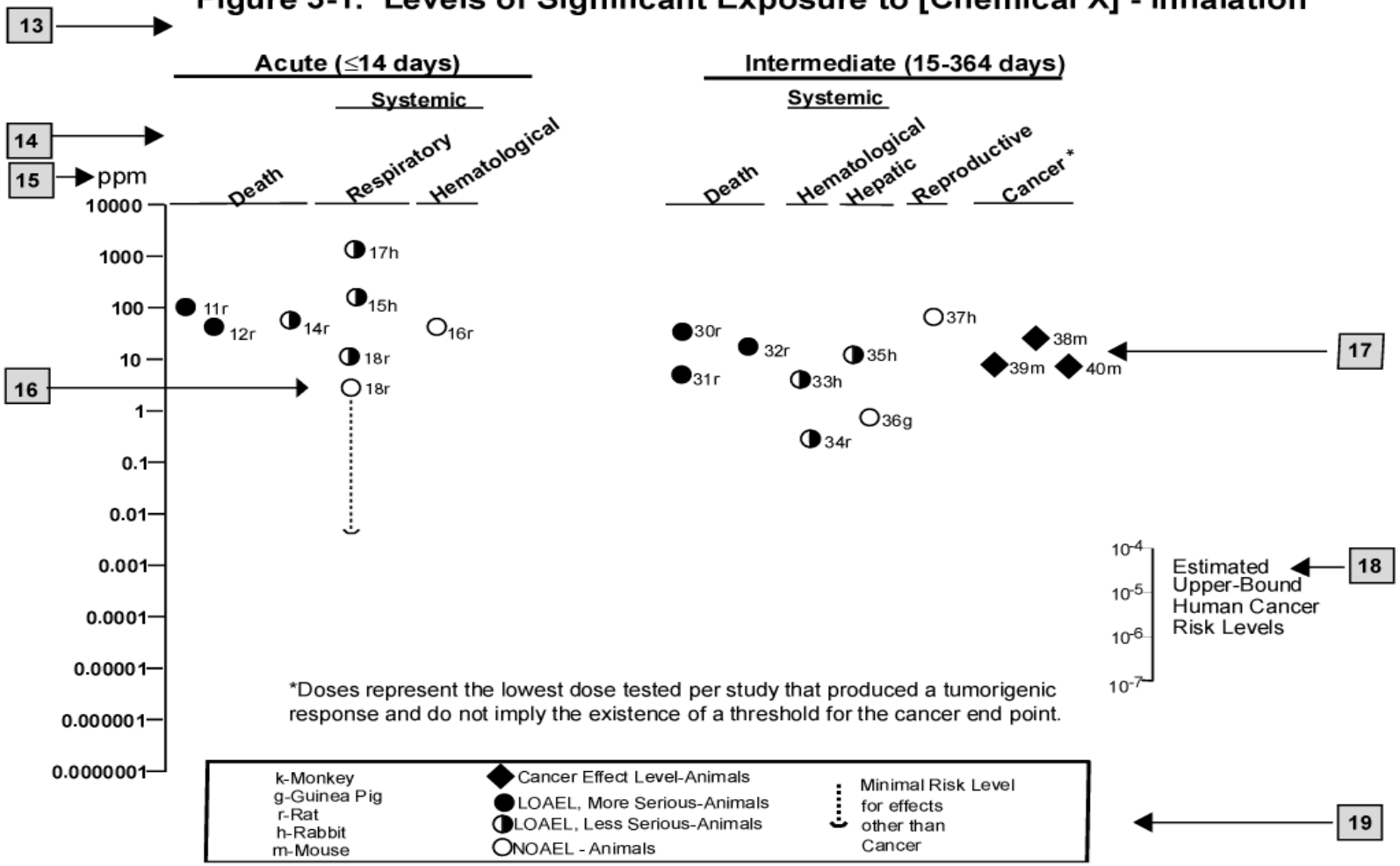
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

	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	↓	↓	↓	↓	↓		↓
4 →	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
	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



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
DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/International 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

APPENDIX D. INDEX