Toxicological Profile for Trichloroethylene

June 2019

U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry

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DISCLAIMER

Use of trade names is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry, the Public Health Service, or the U.S. Department of Health and Human Services.

UPDATE STATEMENT

A Toxicological Profile for Trichloroethylene, Draft for Public Comment was released in October 2014. This edition supersedes any previously released draft or final profile.

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

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Human Health Sciences
Environmental Toxicology Branch
1600 Clifton Road NE
Mailstop S102-1
Atlanta, Georgia 30329-4027

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FOREWORD

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

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for these toxic substances described therein. Each peer-reviewed profile identifies and reviews the most informative (i.e., key) literature that describes a 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 the protection of public health are identified by ATSDR.

Each profile includes the following:

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

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

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

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

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

Patrick N. Breysse, Ph.D., CIH
Director, National Center for Environmental Health and
Agency for Toxic Substances and Disease Registry
Centers for Disease Control and Prevention

*Legislative Background

The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "…effectuate and implement the health related authorities" of the statute. This includes the preparation of 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.
Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the National Priorities List, in an effort to "…establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

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 may 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 (e.g., 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 that for epidemiological studies, there could be multiple routes of exposure.
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:

Chapter 1	**How Can (Chemical X) Affect Children?**
Chapter 1	**How Can Families Reduce the Risk of Exposure to (Chemical X)?**
Section 3.7	**Children's Susceptibility**
Section 6.6	**Exposures of Children**

Other Sections of Interest:

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

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet: http://www.atsdr.cdc.gov

The following additional materials are available online:

Case Studies in Environmental Medicine are self-instructional publications designed to increase primary health care providers' knowledge of a hazardous substance in the environment and to aid in the evaluation of potentially exposed patients (see https://www.atsdr.cdc.gov/csem/csem.html).

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 (see https://www.atsdr.cdc.gov/MHMI/index.asp). 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 (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

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 • Web Page: https://www.cdc.gov/nceh/.

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, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/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 • Web Page: https://www.niehs.nih.gov/.

The National Cancer Institute (NCI) is the federal government's principal agency for cancer research and training. Contact: NCI, BG 9609 MSC 9760, 9609 Medical Center Drive, Bethesda, MD 20892-9760 • Phone: 1-800-4-CANCER (1-800-422-6237).

Clinical Resources (Publicly Available)

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

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

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at http://pehsu.net/findhelp.html.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/.

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CONTRIBUTORS

CHEMICAL MANAGER(S)/AUTHOR(S):

G. Daniel Todd, Ph.D.
Patricia Ruiz, Ph.D.
Moiz Mumtaz, Ph.D.
Jessilynn B. Taylor, M.S.
ATSDR, Division of Toxicology and Human Health Sciences, Atlanta, GA

David W. Wohlers, Ph.D.
Julie Klotzbach, Ph.D.
Gary L. Diamond, Ph.D.
Christina Coley, B.S.
Mario Citra, Ph.D.
SRC, Inc., 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 Environmental Toxicology Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

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

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PEER REVIEW

A peer review panel was assembled for trichloroethylene. The-panel are experts who have knowledge of trichloroethylene'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. The panel consisted of the following members who reviewed prepublic comment draft 3 of the Toxicological Profile for Trichloroethylene:

1. Dr. H.M. Bolt, Professor, Institut für Arbeitsphysiologie an der Universität Dortmund, Dortmund, Germany;

2. Dr. James Bruckner, Department of Pharmaceutical and Biomedical Sciences, College of Pharmacy and Interdisciplinary Toxicology Program, University of Georgia, Athens, Georgia; and

3. Dr. Gloria Post, Research Scientist Office of Science, New Jersey Department of Environmental Protection, Trenton, New Jersey.

In addition, the following reviewers provided comments on the carcinogenicity discussions in postpublic comment draft 2 of the Toxicological Profile for Trichloroethylene:

1. Dr. James Bruckner, Department of Pharmaceutical and Biomedical Sciences, College of Pharmacy and Interdisciplinary Toxicology Program, University of Georgia, Athens, Georgia;

2. Dr. Hermann M. Bolt, Leibniz Research Centre for Working Environmental and Human Factors, Dortmund, Germany; and

3. Dr. Mark Purdue, National Institutes of Health, Bethesda, Maryland.

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 and ATSDR's responses to the comments, exists as part of the administrative record for this compound.

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

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1. PUBLIC HEALTH STATEMENT FOR TRICHLOROETHYLENE

This Public Health Statement summarizes the Agency for Toxic Substances and Disease Registry's (ATSDR) findings on trichloroethylene, including chemical characteristics, exposure risks, possible health effects from exposure, and ways to limit exposure.

The U.S. Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are sites targeted for long-term federal clean-up activities. The EPA has found trichloroethylene in at least 1,051 of the 1,854 current or former NPL sites. The total number of NPL sites evaluated for trichloroethylene is not known. But the possibility remains that as more sites are evaluated, the sites where trichloroethylene is found may increase. This information is important because these future sites may be sources of exposure, and exposure to trichloroethylene may be harmful.

If you are exposed to trichloroethylene, many factors determine whether you'll be harmed. These include how much you are exposed to (dose), how long you are exposed (duration), how often you are exposed (frequency), and how you are exposed (route of exposure). You must also consider the other chemicals you are exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

WHAT IS TRICHLOROETHYLENE?

Trichloroethylene is a colorless, volatile liquid. Liquid trichloroethylene evaporates quickly into the air. It is nonflammable and has a sweet odor.

The two major uses of trichloroethylene are as a solvent to remove grease from metal parts and as a chemical that is used to make other chemicals, especially the refrigerant, HFC-134a. Trichloroethylene has also been used as an extraction solvent for greases, oils, fats, waxes, and tars; by the textile processing industry to scour cotton, wool, and other fabrics; in dry cleaning operations; and as a component of adhesives, lubricants, paints, varnishes, paint strippers, pesticides, and cold metal cleaners.

WHAT HAPPENS TO TRICHLOROETHYLENE WHEN IT ENTERS THE ENVIRONMENT?

Most of the trichloroethylene used in the United States is released into the atmosphere by evaporation, primarily from degreasing operations. Once in the atmosphere, the dominant trichloroethylene

degradation process is reaction with hydroxyl radicals; the estimated half-life for this process is about 3–7 days. This relatively short half-life indicates that trichloroethylene is not a persistent atmospheric compound. Most trichloroethylene in surface waters or on soil surfaces evaporates into the atmosphere, although its high mobility in soil may result in it moving into groundwater below the soil surface. In these subsurface environments, trichloroethylene is only slowly degraded and may be relatively persistent. Trichloroethylene and other volatile organic chemicals may diffuse from contaminated groundwater and soil and migrate into air spaces beneath buildings to enter the indoor air, a process termed vapor intrusion.

HOW MIGHT I BE EXPOSED TO TRICHLOROETHYLENE?

You may be exposed to trichloroethylene from trichloroethylene-contaminated air, water, food, or soil, or direct skin contact. You are most likely to be exposed to trichloroethylene by drinking trichloroethylene-contaminated water; you may also be exposed by breathing trichloroethylene released to the air from trichloroethylene-contaminated water. If you work in the degreasing industry or another industry where trichloroethylene is produced or used, you may be exposed by breathing in trichloroethylene-contaminated air or by contacting the chemical with your skin. Some trichloroethylene is released to the air by its evaporation from products such as adhesives, paints, and coatings; and through its evaporation from trichloroethylene-contaminated soil at landfills.

You may also be exposed to trichloroethylene by consumption of trichloroethylene-contaminated foods, by contact with consumer products containing trichloroethylene, and by direct contact with trichloroethylene-contaminated soil.

HOW CAN TRICHLOROETHYLENE ENTER AND LEAVE MY BODY?

Trichloroethylene can enter your body from trichloroethylene-contaminated air, water, food, or soil.

Trichloroethylene in air can easily enter your body when you breathe. Most of the trichloroethylene that you breathe in will go into your bloodstream and into other organs. A small amount of trichloroethylene in the air can also move through your skin and into your bloodstream.

When trichloroethylene is found in water, it can enter your body when you drink or touch the water or when you breathe in steam from the water. Most of the trichloroethylene that you breathe in or drink will move from your stomach or lungs into your bloodstream. When you touch water containing

trichloroethylene (such as showering or bathing with trichloroethylene-contaminated water), some of it can get through your skin into your body. Also, you can be exposed when trichloroethylene in groundwater evaporates and migrates into air spaces beneath buildings to enter the indoor air, a process termed vapor intrusion, and you breathe that contaminated indoor air.

Trichloroethylene has been detected in table-ready foods at concentrations generally in the range of 2–100 ppb.

You can be exposed to trichloroethylene in soil when small amounts of soil are transferred to your mouth accidentally, when your skin touches the soil, or when you breathe air or dust coming from the soil. You can also be exposed when trichloroethylene in soil evaporates and migrates into air spaces beneath buildings to enter the indoor air, a process termed vapor intrusion, and you breathe that contaminated indoor air.

Once in your blood, your liver changes much of the trichloroethylene into other chemicals. When the body absorbs more trichloroethylene than it can break down quickly, some of the trichloroethylene or its breakdown products can be stored in body fat for a brief period. However, once absorption ceases, trichloroethylene and its breakdown products quickly leave the fat.

You will quickly breathe out much of the trichloroethylene that reaches your bloodstream; most of the trichloroethylene breakdown products leave your body in the urine within a day.

HOW CAN TRICHLOROETHYLENE AFFECT MY HEALTH?

The health effects of trichloroethylene depend on how much trichloroethylene you are exposed to and the length of that exposure. Environmental monitoring data suggest that trichloroethylene levels the public might encounter by direct contact or through air, water, food, or soil, are generally much lower than the levels at which adverse effects are elicited in animal studies. However, some drinking water sources and working environments have been found to contain levels of trichloroethylene that may cause health problems.

Trichloroethylene was once used as an anesthetic for surgery. People who are overexposed to moderate amounts of trichloroethylene may experience headaches, dizziness, and sleepiness; large amounts of trichloroethylene may cause coma and even death. Some people who breathe high levels of

trichloroethylene may develop damage to some of the nerves in the face. Other effects seen in people exposed to high levels of trichloroethylene include evidence of nervous system effects related to hearing, seeing, and balance, changes in the rhythm of the heartbeat, liver damage, and evidence of kidney damage. Some people who get concentrated solutions of trichloroethylene on their skin develop rashes.

Relatively short-term exposure of animals to trichloroethylene resulted in harmful effects on the nervous system, liver, respiratory system, kidneys, blood, immune system, heart, and body weight.

Exposure to trichloroethylene in the workplace may cause scleroderma (a systemic autoimmune disease) in some people. Some men occupationally-exposed to trichloroethylene and other chemicals showed decreases in sex drive, sperm quality, and reproductive hormone levels.

Long-term exposure studies in animals have mainly focused on carcinogenicity and relatively insensitive noncancer end points following oral exposure; these studies are not helpful in defining noncancer end points in humans following long-term exposure. However, depressed body weight and evidence of effects on the thymus were reported in one recent study of mice exposed to trichloroethylene via their mothers during gestation and lactation and via the drinking water for up to 12 months thereafter.

There is strong evidence that trichloroethylene can cause kidney cancer in people and some evidence that it causes liver cancer and malignant lymphoma (a blood cancer). Lifetime exposure to trichloroethylene resulted in increased liver cancer in mice and increased kidney cancer in rats at relatively high exposure levels. There is some evidence for trichloroethylene-induced testicular cancer and leukemia in rats and lymphomas and lung tumors in mice.

The Department of Human Health Services (HHS) has classified trichloroethylene as "*known to be a human carcinogen*" based on sufficient evidence of carcinogenicity from humans. Similarly, the International Agency for Research on Cancer (IARC) has classified it as "carcinogenic to humans" and EPA has characterized it as "carcinogenic in humans by all routes of exposure." These agencies concluded that there were sufficient evidence from human studies that trichloroethylene exposure can cause kidney cancer in humans. There is also some evidence of an association between trichloroethylene exposure and non-Hodgkin's lymphoma in humans.

HOW CAN TRICHLOROETHYLENE AFFECT CHILDREN?

This section discusses potential health effects of trichloroethylene exposure in humans from when they're first conceived to 18 years of age.

Trichloroethylene is expected to affect children in the same manner as adults. It is not known whether children are more susceptible than adults to the effects of trichloroethylene.

Some human studies indicate that trichloroethylene may cause developmental effects such as spontaneous abortion, congenital heart defects, central nervous system defects, and small birth weight. However, these people were exposed to other chemicals as well. In some animal studies, exposure to trichloroethylene during development may have caused effects such as decreased body weight, increased incidences of heart defects, functional or structural changes in the developing nervous system, and effects on the immune system.

HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO TRICHLOROETHYLENE?

If your doctor finds that you have been exposed to significant amounts of trichloroethylene, ask whether your children might also be exposed. Your doctor might need to ask your state health department to investigate. You may also contact the state or local health department with health concerns.

Exposure to contaminated drinking water should be limited. Trichloroethylene has been detected in some drinking water supplies. For bottled water, consumers should contact the bottler with specific questions on potential contaminants.

If you live near an industrial site where trichloroethylene is produced or is a byproduct or you live near a hazardous waste site where it has been discarded, there may be high levels of trichloroethylene in the water and soil. If you find your home water supply and/or soil to be contaminated with trichloroethylene, consider using a cleaner source of water and limiting contact with soil (for example, through use of a dense ground cover or thick lawn) to reduce exposure to trichloroethylene. By paying careful attention to dust and dirt control in the home (air filters, frequent cleaning), you can reduce family exposure to contaminated dirt. Some children eat a lot of dirt. You should prevent your children from eating dirt. You should discourage your children from putting objects in their mouths. Make sure that they wash their hands frequently and before eating. Discourage your children from putting their hands in their mouths or from other hand-to-mouth activity.

Trichloroethylene is widely used as a solvent for extraction, waterless drying, and finishing, and as a general purpose solvent in adhesives, lubricants, paints, varnishes, paint strippers, pesticides, and cold metal cleaners. Follow instructions on product labels to minimize exposure to trichloroethylene.

ARE THERE MEDICAL TESTS TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO TRICHLOROETHYLENE?

Trichloroethylene and its breakdown products (metabolites) can be measured in blood and urine. Because trichloroethylene and its metabolites leave the body fairly rapidly, the tests need to be conducted within a few hours after exposure. Tests for trichloroethylene and its metabolites in the blood or urine require special analytical equipment not readily available at medical facilities. Some metabolites of trichloroethylene can be formed from chemicals other than trichloroethylene, so detection of these metabolites in blood or urine does not guarantee that one has been exposed to trichloroethylene.

For more information on the different substances formed by trichloroethylene breakdown and on tests to detect these substances in the body, see Chapters 3 and 7.

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. Federal agencies that develop regulations for toxic substances include the Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA). Recommendations provide valuable guidelines to protect public health but are not enforceable by law. Federal organizations that develop recommendations for toxic substances include the Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH).

Regulations and recommendations can be expressed as “not-to-exceed” levels; that is, levels of a toxic substance in air, water, soil, or food that do not exceed a critical value usually based on levels that affect animals; levels are then adjusted to help protect humans. Sometimes these not-to-exceed levels differ among federal organizations. Different organizations use different exposure times (e.g., an 8-hour workday or a 24-hour day), different animal studies, or emphasize some factors over others, depending on their mission.

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

EPA set a maximum contaminant level goal (MCLG) of zero as a national primary drinking standard for trichloroethylene; EPA noted liver problems and increased risk of cancer as potential health effects from long-term exposure above the maximum contaminant level (MCL) of 0.005 milligrams per liter (mg/L; 5 ppb).

OSHA set a permissible exposure limit (PEL) of 100 ppm for trichloroethylene in air averaged over an 8-hour work day, an acceptable ceiling concentration of 200 ppm provided the 8-hour PEL is not exceeded, and an acceptable maximum peak of 300 ppm for a maximum duration of 5 minutes in any 2 hours.

NIOSH considers trichloroethylene to be a potential occupational carcinogen and established a recommended exposure limit (REL) of 2 ppm (as a 60-minute ceiling) during the usage of trichloroethylene as an anesthetic agent and 25 ppm (as a 10-hour time-weighted average [TWA]) during all other exposures.

WHERE CAN I GET MORE INFORMATION?

If you have any questions or concerns, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below. You may also contact your doctor if experiencing adverse health effects or for medical concerns or questions. ATSDR can also provide publicly available information regarding medical specialists with expertise and experience recognizing, evaluating, treating, and managing patients exposed to hazardous substances.

- Call the toll-free information and technical assistance number at 1-800-CDCINFO (1-800-232-4636) or

- Write to:
  Agency for Toxic Substances and Disease Registry
  Division of Toxicology and Human Health Sciences
  1600 Clifton Road NE
  Mailstop S102-1
  Atlanta, GA 30329-4027

Toxicological profiles and other information are available on ATSDR's web site: http://www.atsdr.cdc.gov.

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO TRICHLOROETHYLENE IN THE UNITED STATES

Trichloroethylene is a major nonflammable industrial solvent. In 2011, the estimated capacity of the commercial production of trichloroethylene in the United States was 270 million pounds. Historically, the most important use of trichloroethylene has been vapor degreasing of metal parts. This use has declined over the past decade due to increased environmental regulations governing trichloroethylene emissions. At the same time, trichloroethylene has found increasing use as a feedstock for the refrigerant, HFC-134a. Trichloroethylene is also widely used as a solvent for extraction, waterless drying and finishing, and as a general purpose solvent in adhesives, lubricants, paints, varnishes, paint strippers, pesticides, and cold metal cleaners. Trichloroethylene was used in the dry cleaning industry; although its general use in this industry was discontinued in the 1950s, it continued to be used in some spot removing products (Bakke et al. 2007; EPA 2017; IARC 2014). EPA (2017) has proposed banning uses of trichloroethylene in aerosol degreasers and spot cleaners.

Trichloroethylene is released to the environment during the course of its manufacture, formulation, and use. It is frequently detected in the atmosphere and in water. In 2017, environmental releases of trichloroethylene reported under the EPA Toxics Release Inventory (TRI) program were 1,886,809 pounds (855.8 metric tons) in air emissions, 34 pounds (0.02 metric tons) in surface water discharges, 115,793 pounds (52.5 metric tons) in releases to soil, and 3,723 pounds (1.7 metric tons) in releases via underground injection.

The most important routes of exposure to trichloroethylene for most members of the general population are inhalation of the compound in ambient air and ingestion of drinking water. Trichloroethylene may evaporate from contaminated groundwater and soil and migrate into air spaces beneath buildings to enter the indoor air, a process termed vapor intrusion. Mean trichloroethylene concentrations measured in air at locations across the United States are generally between 0.01 and 0.3 ppb, although mean levels as high as 3.4 ppb have been reported. Workers, particularly in the degreasing industry, are exposed by inhalation to the highest levels of trichloroethylene, ranging from approximately 1 to 100 ppm. Between 4.5 and 18% of the drinking water supply sources in the United States that are tested on a yearly basis by the EPA have measurable levels of trichloroethylene; these levels are typically <30 ppb. The general population can also be exposed to trichloroethylene by consumption of contaminated foods and by contact

with consumer products containing the compound. Trichloroethylene levels in the low ppb range have been measured in food; however, levels as high as 140 ppb were measured in a few samples.

Data from the National Health and Nutrition Examination Survey (NHANES) show that levels of trichloroethylene were generally below the detection limit of 0.012 ng/mL (ppb) in the blood of 17,419 members of the U.S. general population sampled between 2001 and 2014. Details of the results may be found in Section 6.5.

2.2 SUMMARY OF HEALTH EFFECTS

Available human and animal data indicate that the central nervous system is a target for trichloroethylene toxicity. Acute overexposure to trichloroethylene vapors results in effects that may include central nervous system depression, loss of consciousness, and even death. Available human and animal data identify the kidney, liver, immune system, male reproductive system, and developing fetus as other potential targets of trichloroethylene toxicity. Results from available animal studies suggest that the immune system and developing fetus may represent particularly sensitive targets of trichloroethylene toxicity. Trichloroethylene has been shown to cause dermal and ocular irritation and depressed body weight gain. Increased incidences of tumors in the kidney, liver, and lymphoid tissues have been reported in chronic bioassays of rats and mice exposed to very high levels of trichloroethylene via inhalation and oral exposure routes. Available human data provide strong support for trichloroethylene-induced kidney cancer and somewhat lesser support for trichloroethylene-induced liver cancer and malignant lymphoma in humans. The systemic effects elicited by trichloroethylene are not exposure-route-specific; similar effects can be elicited via oral and inhalation exposure routes. Physiologically-based pharmacokinetic (PBPK) models have been developed and used for route-to-route extrapolation (i.e., for a given effect elicited at a particular exposure level via one exposure route [inhalation or oral], PBPK modeling can predict the exposure level at which the same effect would be induced via the other exposure route). PBPK models have also been employed to predict exposure levels in humans that would result in effects similar to those observed in rodents.

Neurological Effects. Reported neurological effects that have been associated with substantial exposure to trichloroethylene include euphoria, giddiness, lethargy, confusion, subjective symptoms of vestibular impairment (dizziness, headache, nausea), difficulty swallowing, facial effects that indicate possible trigeminal nerve damage (including sensation deficits, jaw weakness, increased blink reflex latency), dysfunction of cranial nerves other than the trigeminal nerve, memory deficits, impaired hearing,

impaired visual function, mood swings, muscle weakness, tremor, decreased psychomotor function, psychotic behavior, impaired cognitive function, and loss of consciousness.

Neurological effects similar to those associated with trichloroethylene exposure in humans have been reported in laboratory animals following acute or repeated inhalation or oral exposures. Short-term oral administration of trichloroethylene to rats resulted in morphological changes in the trigeminal nerve. Increased handling reactivity and increased sleep time (considered possible indicators of mood disturbances) were reported in rats repeatedly exposed to trichloroethylene. Other animal studies reported trichloroethylene-induced neuropathy, auditory impairment, visual impairment, impaired cognitive function, changes in some measures of psychomotor function, behavioral effects, cardiac arrhythmia, and neurochemical or molecular changes.

Cancer. The potential carcinogenicity of inhaled trichloroethylene has been evaluated in numerous epidemiological studies and experimental animal studies. HHS has classified trichloroethylene as "*known to be a human carcinogen*" based on sufficient evidence of carcinogenicity from humans. NTP specifically concluded that trichloroethylene causes kidney cancer in humans based on consistent results of epidemiological studies and has a causal association with non-Hodgkin's lymphoma based on results of several epidemiological studies; however, the epidemiological evidence for non-Hodgkin's lymphoma is less consistent than for kidney cancer. For other cancer types, NTP concluded that evidence from epidemiological studies is inadequate to evaluate associations. IARC has classified trichloroethylene as "carcinogenic to humans" based on sufficient evidence in humans (Group 1), concluding that the epidemiological evidence for kidney cancer is sufficient to establish a causal relationship, and "positive associations" have been observed for non-Hodgkin's lymphoma and liver cancer. EPA has characterized trichloroethylene as "carcinogenic in humans by all routes of exposure." EPA conclusions regarding epidemiological evidence for cancer are similar to the conclusions of NTP: convincing evidence for a causal relationship for trichloroethylene and kidney cancer; strong evidence for a causal relationship for non-Hodgkin's lymphoma, but less consistent that that for kidney cancer; limited evidence for liver cancer; and less evidence for other cancer types.

Hepatic Effects. There is some evidence for trichloroethylene-induced hepatic effects in occupationally-exposed humans; however, limitations generally include lack of quantifiable exposure data and concomitant exposure to other chemicals. Some studies reported changes in blood and urine indices of liver function and enlarged livers in persons occupationally exposed to trichloroethylene.

Where liver effects were observed, exposure levels were likely higher than present-day occupational exposure limits.

Case reports provide more convincing evidence of trichloroethylene-induced hepatic effects in humans. A 37-year-old male with occupational exposure to trichloroethylene and a reportedly unprotected high-level acute exposure to trichloroethylene vapors during the preparation of a solvent mixture presented to a hospital in a jaundiced condition and died several weeks later; acute massive liver necrosis was noted at autopsy. Acute hepatic necrosis was also seen in a degreaser who died after being exposed to trichloroethylene for at least 6 weeks and in another man who had accidentally ingested an unknown amount of trichloroethylene. Two case studies of people hospitalized after intentional acute inhalation of very high concentrations of trichloroethylene showed liver damage at autopsy in one and hepatocyte degeneration revealed by liver biopsy in the other. Liver effects such as jaundice, hepatomegaly, hepatosplenomegaly, hepatitis, and liver failure have been reported in patients with occupational or nonoccupational exposure to trichloroethylene.

Dose-related increases in liver weight and hepatocellular hypertrophy have been consistently reported in trichloroethylene-exposed animals. Increasing severity of liver necrosis with dose was also seen in other studies. Indicators of trichloroethylene-induced peroxisomal proliferation have been reported in both rats and mice; mice appear to be somewhat more sensitive than rats. Relatively high exposure levels were necessary to induce hepatic effects in most animal studies.

Renal Effects. Renal toxicity, as indicated by changes in urinary proteins and N-acetyl-β-d-glucos-aminidase (NAG), was noted in workers exposed to trichloroethylene and other chemicals in the workplace. Changes in urinary proteins were also observed in renal cancer patients with reported exposure to trichloroethylene. A retrospective cohort study of end-stage renal disease in aircraft workers exposed to trichloroethylene and other hydrocarbons reported increased risk for trichloroethylene-related end-stage renal disease. No clear evidence of kidney effects has been reported in studies examining the association of long-term exposure to trichloroethylene in drinking water and adverse health effects.

Acute inhalation exposure of rats to high concentrations of trichloroethylene resulted in increases in urinary glucose, proteins, glucosaminidase, gamma glutamyl transpeptidase, and serum urea nitrogen. Following intermediate-duration (>14 days, but <1 year) inhalation exposure of animals to trichloroethylene, increased kidney weights were observed. Chronic-duration (lifetime) inhalation exposure of rats to trichloroethylene resulted in renal tubular megalonucleocytosis in males but not

females. Mild to moderate cytomegaly and karyomegaly in the renal tubular epithelial cells were observed in an intermediate-duration oral study in mice. Following intermediate-duration oral exposure, effects noted included increased kidney weights, elevated urinary protein and ketones, minimal to mild cytomegaly, and karyomegaly of the renal tubular epithelial cells. Treatment-related nephropathy was observed in rats and mice following chronic oral exposure to trichloroethylene. Rats appeared to be more sensitive than mice. The observed nephropathy was described as cytomegaly, megalonucleocytosis, and degenerative/regenerative tubular alterations dissimilar to lesions characteristic of chronic nephropathy commonly noted in aged animals.

Immunological and Lymphoreticular Effects. Dermal effects in persons occupationally exposed to trichloroethylene may be sensitivity reactions (termed Stevens-Johnson syndrome) in many cases and may include effects on mucous membranes. Other immunological effects observed in occupational settings include decreased numbers of total lymphocytes and selected lymphocyte subsets in blood samples from workers exposed to trichloroethylene that was used for cleaning a variety of materials and products, altered serum inflammatory cytokine levels, and decreases in serum IgG and IgM.

People who drank trichloroethylene-contaminated water in Woburn, Massachusetts, had immunological abnormalities, but these people were also exposed to other volatile chlorinated hydrocarbons in the water. Symptoms of systemic lupus erythematosus were increased in residents of Tucson, Arizona, exposed to trichloroethylene and other chemicals in drinking water. Diffuse fasciitis with eosinophilia (clinically and histologically distinct from scleroderma) was reported in a woman who used well water contaminated with trichloroethylene. The trichloroethylene level was measured at 14 ppm (2,800 times higher than the maximum permissible contaminant level of 0.005 ppm). The woman's condition improved after she started using bottled drinking water.

There is some evidence for an association between occupational exposure to trichloroethylene and the occurrence of scleroderma (systemic sclerosis, a chronic autoimmune disease primarily of the skin). A meta-analysis of these studies indicated increased risk of scleroderma for any exposure to trichloroethylene in men and women. It should be noted that the incidence of scleroderma in women is, on average, 3 times higher than in men, thus making detection of small increases in rate difficult in women.

Results of several animal studies indicate that selected allergic or hypersensitivity reactions are enhanced following oral exposure to trichloroethylene. Exposure of rats and mice to trichloroethylene in the

drinking water resulted in an enhancement of antigen-stimulated reactions. Increased hypersensitivity responses were observed in male mouse pups that had been sensitized by subcutaneous injection of sheep red blood cells (SRBCs) and exposed to trichloroethylene via their mothers during gestation and lactation and postnatally from the drinking water.

Trichloroethylene-induced acceleration of autoimmune disease has been demonstrated in autoimmune-prone strains of mice; reported effects include changes in cytokine levels, autoimmune hepatitis, inflammatory skin lesions, and alopecia. B6C3F1 mice (not particularly susceptible to autoimmune disease) exhibited increased anti-double-stranded deoxyribonucleic acid (DNA) antibodies when exposed to trichloroethylene as adults and decreased thymus weight and decreased plaque-forming cell response when exposed prenatally or neonatally. A decrease in plaque-forming cell response was observed in Sprague-Dawley rats repeatedly exposed to trichloroethylene vapors for 4 weeks at 1,000 ppm.

Animal studies provide some evidence of trichloroethylene-induced immunosuppression. Effects associated with inhalation exposure to trichloroethylene include reduced splenic anti-SRBC IgM response in female rats, decreased serum IgM levels, liver inflammation, splenomegaly, and hyperplasia of lymphatic follicles in an autoimmune-prone strain of male mice, and depressed resistance to *Streptococcus zooepidemicus*. Another animal study, in which mice were exposed to trichloroethylene in the drinking water, showed treatment-related decreases in both cellular- and antibody-mediated immunity; however, the effects did not occur consistently or in a dose-dependent manner.

Reproductive Effects. Possible associations between exposure to organic solvents (including trichloroethylene) and measures of fertility and fecundity have been assessed to some extent in occupationally-exposed men and women. Suggestive evidence of an association between exposure to trichloroethylene and adverse female reproductive outcomes includes reports of reduced fecundability and menstrual cycle disturbances (including amenorrhea). Evidence of trichloroethylene-induced effects in occupationally-exposed men includes reports of decreased potency, altered sex drive or function, decreased sperm quality, and decreased serum levels of reproductive hormones.

Studies in animals demonstrate the toxicity of trichloroethylene to the male reproductive system. Repeated exposures of male rats or mice to high doses of trichloroethylene resulted in effects such as degeneration of epididymal epithelium, decreased sperm quality, testicular atrophy, histopathologic lesions of the testes or epididymides, decreased sperm count and motility, epididymal epithelial damage, decreased serum hormone levels, impaired libido/copulatory behavior, and decreased numbers of sperm

capable of attaching to eggs *in vitro*. Reproductive performance was not tested in most of the animal studies.

Developmental Effects. The potential for trichloroethylene-induced developmental effects in humans has been assessed to some extent. Epidemiological data are typically limited by concomitant exposure to other potentially hazardous substances, and case-control studies are limited by small numbers of cases. Evidence for trichloroethylene-induced developmental effects in humans derives from studies that evaluated exposures to trichloroethylene in workplace or residential environments or from the drinking water.

In one retrospective case-control study, a 3-fold increased rate of spontaneous abortion was reported among women who had been occupationally or nonoccupationally exposed to trichloroethylene (and other solvents) compared to a group of women without trichloroethylene exposure. Other case-control studies found no evidence of increased risk of spontaneous abortion with occupational or nonoccupational exposure of the women or their husbands to trichloroethylene. However, these studies are limited by small numbers of spontaneous abortion. ATSDR found no support for an association between living in an area around Endicott, New York, where residents may have been exposed to volatile organic compounds (including trichloroethylene) via soil vapor intrusion into homes, and rates of spontaneous fetal death. In another study of the same area around Endicott, New York, elevated risk was reported for low birth weight, small for gestational age, term low birth weight, cardiac defects, and conotruncal defects. A 3-fold increased risk of congenital heart defects was reported for women living within 1.32 miles of at least one trichloroethylene-emitting site in the area of Milwaukee, Wisconsin, compared to those living outside the 1.32 mile radius; however, the risk was increased only among those women who were ≥38 years old at delivery. Proximity to trichloroethylene-emitting sites was not of itself a significant factor for risk of congenital heart defects in this study. In a birth outcome analysis conducted in the area of Endicott, New York, where residents may have been exposed to volatile organic compounds (including trichloroethylene) via soil vapor intrusion into homes, total cardiac defects were twice as prevalent as expected. This finding was not linked to trichloroethylene exposure *per se*, and the results did not support an association between living in the study area and increased risk of fetal death. One study reported a 2.5-fold increase in rate of congenital heart disease in children whose parents were exposed to trichloroethylene in the drinking water during the month before conception and the first trimester of pregnancy. Moreover, the rate of congenital heart disease decreased after the trichloroethylene-contaminated wells were shut down. There was suggestive evidence of an association between trichloroethylene exposure and cardiac defects in a survey conducted within an area of New Jersey that

was serviced with trichloroethylene-contaminated public drinking water. Other studies found no association between exposure to trichloroethylene from the drinking water and heart defects.

A small effect on birth weight was noted in a report on adverse birth outcomes for a population living at Camp Lejeune, North Carolina. The study authors reported strong associations between long-term maternal exposure to trichloroethylene in the range of 1 ppm and decreased mean body weight and small for gestational age in male (but not female) infants. The result is limited by small sample size (only 31 total births in the trichloroethylene-exposed group). There was no conclusive effect on birth weight in other studies of individuals exposed to trichloroethylene in the drinking water.

Other developmental effects that have been associated with trichloroethylene in the drinking water include ocular and auditory defects and other central nervous system abnormalities, oral cleft, choanal atresia (a rare respiratory disorder) and hypospadias/congenital chordee, and developmental immunosuppression (reduction in Th1 IL-2 producing T-cells). However, most of these studies are limited in statistical power due to small numbers of cases.

Decreased fetal weight was noted in offspring of rats exposed to 1,800 ppm trichloroethylene vapors 6 hours/day on gestation days (GDs) 0–20. Effects such as decreases in litter size and perinatal survival have been reported in rats at maternally toxic oral doses. Increased incidences of cardiac malformations were observed in fetuses of rat dams exposed to trichloroethylene in the drinking water during premating and gestation or gestation alone at non-maternally toxic concentrations (estimated doses of 0.218, 0.25, and 129 mg/kg/day), but not in fetuses of rat dams administered gavage doses of trichloroethylene during GDs 6–15 at 500 mg/kg/day. The basis for conflicting results regarding trichloroethylene-induced cardiac malformations in the animal studies is not clear; however, it may be due, in part, to differences in procedures used to evaluate fetal cardiac morphology and/or the relative ability to detect cardiac malformations.

Functional alterations were observed in the immune system of young mice exposed to trichloroethylene via their mothers during gestation and postnatal periods via lactation or direct exposure in the drinking water.

Trichloroethylene-induced neurodevelopmental toxicity has been assessed in young animals that were exposed either during *in utero* development via their mothers, or by direct oral exposure during postnatal development. Reduced rearing was reported in young male mice receiving trichloroethylene orally at

doses of 50 and 290 mg/kg/day during postnatal days 10–16. Dose-related altered open-field activity was noted in young rats whose mothers had received dietary trichloroethylene at 75–300 mg/kg/day during gestation and lactation. Other studies have reported decreases in numbers of myelinated fibers, decreased glucose uptake in the brain, and increased activity in the offspring of rats receiving trichloroethylene at an estimated oral dose level of 37 mg/kg/day during premating, mating, gestation, and lactation.

Cardiovascular Effects. Chronic cardiovascular disease has not been reported in workers occupationally exposed to low levels of trichloroethylene, although deaths following acute high-level inhalation exposures to trichloroethylene have been attributed to cardiac arrhythmias. Case studies have described cardiac arrhythmias that in some instances led to death after occupational exposure, or anesthesia. Accidental oral exposure to trichloroethylene has resulted in cardiac arrythmias. Cardiac arrhythmias reported in a small number of people who drank from contaminated wells could not be attributed to trichloroethylene alone. Increased congenital heart defects were noted in another population exposed to trichloroethylene in their drinking water, but a cause-and-effect relationship could not be established. When compared with a national sample, excess of stroke was consistently reported in ATSDR Trichloroethylene Subregistry baseline and follow-up reports of persons environmentally exposed to trichloroethylene. However, inherent limitations in study design preclude establishment of a cause-and-effect relationship.

Studies in laboratory animals have indicated that trichloroethylene-induced cardiac sensitization to catecholamines may explain the arrhythmias that have been documented in humans exposed to high vapor concentrations of this agent. Cardiac arrhythmias were reported in rats exposed to trichloroethylene. Exposure to trichloroethylene has been correlated with cardiac abnormalities in developing chick embryos as well as rat fetuses. Histopathological changes in the heart have not been observed in animals exposed to trichloroethylene following intermediate-duration exposure periods. Changes in serum polyunsaturated fatty acid ratios, which are implicated in cardiovascular disease, have been observed in rats exposed to 300 ppm trichloroethylene vapor for 12 weeks.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for trichloroethylene. 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-duration exposure (≤14 days), intermediate-duration exposure (15–364 days), and chronic duration exposure (≥365 days) 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.

ATSDR reviewed and concurred with the approach presented by EPA for their reference dose (RfD) and reference concentration (RfC) (EPA 2011e). The RfD and RfC are based on the results of oral exposure studies that reported impaired immune function in mice (RfD only) (Peden-Adams et al. 2006), decreased thymus weight in female mice (Keil et al. 2009), and fetal heart malformations in rats (Johnson et al. 2003). EPA used PBPK modeling to calculate internal dose points of departure (idPODs) and to perform route-to-route extrapolation (RfC only) (EPA 2011e). Potential points of departure (PODs) for candidate chronic RfC and RfD values for numerous studies were determined by utilizing the lowest-observed-adverse-effect level (LOAEL)/no-observed-adverse-effect level (NOAEL) approach, benchmark dose (BMD) analysis, and/or physiologically based pharmacokinetic (PBPK) modeling of human and animal data considered suitable for dose-response assessment (EPA 2011e; IRIS 2011). Candidate critical effects included trichloroethylene-induced neurological effects in humans and animals (Albee et al. 2006; Arito et al. 1994a; Barret et al. 1992; Blain et al. 1994; Crofton and Zhao 1997; Gash et al. 2008; Isaacson et al. 1990; Kjellstrand et al. 1987; Kulig 1987; Mhiri et al. 2004; Moser et al. 1995; Nunes et al. 2001; Rebert et al. 1991; Ruijten et al. 1991; Waseem et al. 2001); effects on kidney, liver, and body weight in animals (Boverhof et al. 2013; Buben and O'Flaherty 1985; Kjellstrand et al. 1983b; Maltoni et al. 1986; NCI 1976; NTP 1988, 1990); immunological effects in animals (Boverhof et al. 2013; Cai et al. 2008; Griffin et al. 2000a, 2000b; Kaneko et al. 2000; Keil et al. 2009; Sanders et al. 1982); reproductive effects in humans and animals (Chia et al. 1996; DuTeaux et al. 2004; Forkert et al. 2002; Kan et al. 2007; Kumar et al. 2000a, 2001b; Land et al. 1981; Manson et al. 1984; Narotsky et al. 1995; NTP 1985, 1986; Schwetz et al. 1975; Xu et al. 2004; Zenick et al. 1984); and developmental effects in animals

(Fredriksson et al. 1993; Healy et al. 1982; Isaacson and Taylor 1989; Johnson et al. 2003; Manson et al. 1984; NTP 1985, 1986; Narotsky et al. 1995; Peden-Adams et al. 2006; Taylor et al. 1985).

A PBPK model was employed to calculate an idPOD for plausible internal dose-metrics based on present understanding of the role that different trichloroethylene metabolites play in trichloroethylene toxicity and the mode of action for toxicity. The PBPK model was used to estimate interspecies and intraspecies pharmacokinetic variability and resulted in 99th percentile estimates of human equivalent dose (HED_{99}) or human equivalent concentration (HEC_{99}) for candidate critical effects (EPA 2011e). The PBPK modeling exercise simulated 100 weeks of exposure for humans and was considered representative of continuous lifetime exposure for humans because longer simulations did not add substantially to the average (e.g., doubling the simulated exposure time resulted in less than a few percent change in the resulting HED). The PBPK model was not used for one study that included a complex exposure scenario in which mouse dams were administered trichloroethylene in the drinking water during gestation and lactation and pups were subsequently exposed via their drinking water (Peden-Adams et al. 2006) because no adequate model parameters were available for this exposure scenario.

Oral MRLs. The available database for trichloroethylene was considered adequate for derivation of chronic- and intermediate-duration oral MRLs, which are briefly presented below; see Appendix A for additional information on these values. The database was not considered adequate for derivation of an acute-duration oral MRL.

Chronic-Duration Oral MRL. The chronic-duration oral MRL is based on the results of three critical oral exposure studies that reported immunotoxicity (decreased plaque-forming cell response and increased delayed-type hypersensitivity) in mice (Peden-Adams et al. 2006), decreased thymus weight in female mice (Keil et al. 2009), and fetal heart malformations in rats (Johnson et al. 2003). In the EPA assessment for trichloroethylene (EPA 2011e), independent candidate chronic RfD values were calculated for each of these effects. The Peden-Adams et al. (2006) immunotoxicity LOAEL of 0.37 mg/kg/day was divided by a total uncertainty factor of 1,000 (to account for use of a LOAEL, interspecies extrapolation, and human variability), resulting in a candidate chronic RfD of 0.00037 mg/kg/day. The Keil et al. (2009) thymus weight LOAEL of 0.35 mg/kg/day was used to derive a PBPK model-based human equivalent dose (HED_{99}) of 0.048 mg/kg/day, which was divided by a total uncertainty factor of 100 (to account for use of a LOAEL, interspecies extrapolation, and human variability using a PBPK model), resulting in a candidate chronic RfD of 0.00048 mg/kg/day. The Johnson et al. (2003) fetal heart malformation data were subjected to benchmark dose analysis. The resulting $BMDL_{01}$ (1% extra risk) of

0.0207 mg/kg/day was used to calculate a PBPK model-based HED_{99} of 0.0051 mg/kg/day, which was divided by a total uncertainty factor of 10 (to account for interspecies extrapolation and human variability using a PBPK model). The resulting candidate chronic RfD was 0.00051 mg/kg/day. EPA (2011e) elected to use a chronic RfD value of 0.0005 mg/kg/day and noted that this value was supported by results for multiple effects. ATSDR agreed that this was a reasonable approach. Therefore, the chronic-duration oral MRL is 0.0005 mg/kg/day.

Intermediate-Duration Oral MRL. ATSDR has adopted the chronic-duration oral MRL of 0.0005 mg/kg/day as the intermediate-duration oral MRL for trichloroethylene. The PBPK model used to calculate the idPOD for the chronic value utilized a 100-week simulation to represent continuous lifetime exposure for humans. Sample simulations for a 52-week exposure (within the range of an ATSDR-defined intermediate-duration exposure [15–364 days]) resulted in the same idPOD as the idPOD from the simulation using the 100-week exposure. It should be noted that the co-critical studies (Johnson et al. 2003; Keil et al. 2009; Peden-Adams et al. 2006), which served as basis for the chronic-duration oral MRL for trichloroethylene, each employed intermediate-duration oral exposure.

Acute-Duration Oral MRL. An acute-duration oral MRL was not derived for trichloroethylene due to the lack of adequate human or animal data for exposures ≤14 days in duration. Intermediate-duration oral gestational or early postnatal exposure studies have reported sensitive developmental effects (e.g., cardiac malformations, developmental immunotoxicity). These effects could potentially be elicited by trichloroethylene exposure for <15 days if exposure were to occur during critical periods of development; acute-duration studies have not investigated these potential outcomes. Derivation of an acute-duration oral MRL based on a less sensitive effect might underestimate the health concern. Therefore, using a conservative approach, the intermediate-duration oral MRL for trichloroethylene based on developmental effects is considered protective for acute-duration oral exposure as well.

Inhalation MRLs. The available database for trichloroethylene was considered adequate for derivation of chronic- and intermediate-duration inhalation MRLs, which are briefly presented below; see Appendix A for additional information on these values. The database was not considered adequate for derivation of an acute-duration inhalation MRL.

Chronic-Duration Inhalation MRL. The chronic-duration inhalation MRL is based on the results of two critical oral exposure studies that reported decreased thymus weight in female mice (Keil et al. 2009) and fetal heart malformations in rats (Johnson et al. 2003). In the EPA assessment for trichloroethylene (EPA

2011e), EPA developed a PBPK model, which was used to calculate the idPOD and perform route-to-route extrapolation to human equivalency concentrations (HECs) for these studies. The resulting HEC_{99} values were 0.033 ppm based on thymus weight and 0.0037 ppm based on fetal heart malformations. The HEC_{99} of 0.033 ppm for thymus weight was divided by a total uncertainty factor of 100 (to account for use of a LOAEL and to account for species extrapolation and human variability using a PBPK model); the resulting candidate chronic RfC was 0.00033 ppm. The HEC_{99} of 0.0037 ppm for fetal heart malformations was divided by a total uncertainty factor of 10 (to account for species extrapolation and human variability using a PBPK model); the resulting candidate chronic RfC was 0.00037 ppm. EPA (2011e) selected the midpoint value of the studies (0.0004 ppm, rounded up from 0.00035 ppm) as the chronic RfC for trichloroethylene. ATSDR agreed that this was a reasonable approach. The resulting chronic-duration inhalation MRL is 0.0004 ppm.

Intermediate-Duration Inhalation MRL. ATSDR has adopted the chronic-duration inhalation MRL of 0.0004 ppm as the intermediate-duration inhalation MRL for trichloroethylene. The PBPK model used to calculate the idPOD for the chronic value utilized a 100-week simulation to represent continuous lifetime exposure for humans. Sample simulations for a 52-week exposure (within the range of an ATSDR-defined intermediate-duration exposure [15–364 days]) resulted in the same idPOD as the idPOD from the simulation using the 100-week exposure. It should be noted that the co-critical studies (Johnson et al. 2003; Keil et al. 2009), which served as basis for the MRL, employed intermediate-duration oral exposure.

Acute-Duration Inhalation MRL. An acute-duration inhalation MRL was not derived for trichloroethylene due to the lack of adequate human or animal data for exposures via inhalation (or PBPK model-extrapolated results from oral studies) of ≤14 days in duration. Intermediate-duration oral gestational or early postnatal exposure studies have reported sensitive developmental effects (e.g., cardiac malformations, developmental immunotoxicity). These effects could potentially be elicited by trichloroethylene exposure for <15 days if exposure were to occur during critical periods of development; acute-duration inhalation studies have not investigated these potential outcomes. Derivation of an acute-duration inhalation MRL based on a less sensitive effect might underestimate the health concern.

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3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of trichloroethylene. 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 (e.g., death, systemic, immunological, neurological, reproductive, developmental, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

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

the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

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

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of trichloroethylene are indicated in Tables 3-1 and 3-3 and Figures 3-1 and 3-17.

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

Humans have died from breathing high concentrations of trichloroethylene fumes. Most of the reported deaths have been associated with accidental breathing of unusually high levels of trichloroethylene vapors in the workplace during its use in cleaning, degreasing, dry cleaning, or construction operations (Bell 1951; Coopman et al. 2003; Ford et al. 1995; James 1963; Kleinfeld and Tabershaw 1954; McCarthy and Jones 1983; Pantucharoensri et al. 2004; Smith 1966; Thorburn et al. 2004). A number of the deaths occurred after the trichloroethylene exposure ended and involved physical exertion that may have contributed to the sudden deaths (Smith 1966; Troutman 1988). Deaths have also resulted from the early use of trichloroethylene as an anesthetic (DeFalque 1961) as well as the presumed intentional inhalation of concentrated fumes from trichloroethylene-containing substances (Clearfield 1970; Jones and Singer 2008; Takaki et al. 2008; Troutman 1988). Death associated with liver damage has also been reported in persons occupationally exposed to trichloroethylene for intermediate and chronic durations, followed by a high acute-duration exposure (Joron et al. 1955; Priest and Horn 1965). None of these cases provided adequate exposure level or duration data to define with accuracy the levels of inhalation exposure that cause human deaths.

In a cohort mortality study of 14,457 aircraft maintenance workers employed for at least 1 year between 1952 and 1956, a significant excess of death from asthma was found among 6,153 workers with reported occupational exposure to trichloroethylene; however, the workers were likely exposed to other chemicals as well (Blair et al. 1998).

Animal experimentation has revealed inhaled concentrations that result in death following acute, intermediate, and chronic exposures. An LC_{50} value for acute exposure in rats was reported as 12,500 ppm for a 4-hour exposure (Siegel et al. 1971). Two out of 10 mice died after a 4-hour exposure to 6,400 ppm trichloroethylene (Kylin et al. 1962). Death was often caused by the central nervous system depression that occurs with very high exposure levels. Data on the lethality of longer-term exposure to trichloroethylene have been provided by studies of intermediate and chronic duration. Laboratory animals (rats, guinea pigs, monkeys, rabbits, and dogs) survived intermittent exposure to 700 ppm for 6 weeks or continuous exposure to 35 ppm for 90 days (Prendergast et al. 1967). There was no decrease in survival for rats and hamsters exposed to 500 ppm for 18 months, although a significant decrease in survival was seen for mice exposed to 100 ppm for the same amount of time (Henschler et al. 1980).

All reliable LOAEL and LC_{50} values for death in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.2 Systemic Effects

The highest NOAEL values and all LOAEL values from each reliable study for each species, duration, and end point for systemic effects are recorded in Table 3-1 and plotted in Figure 3-1.

Respiratory Effects. A worker developed labored breathing and respiratory edema after welding stainless steel that had been washed in trichloroethylene (Sjogren et al. 1991). The effects were attributed to inhalation of the trichloroethylene decomposition products, phosgene and dichloroacetyl chloride, although a history of cigarette smoking may have predisposed the subject to these respiratory effects. In a cohort mortality study of 14,457 aircraft maintenance workers employed for at least 1 year between 1952 and 1956, a significant excess of death from asthma (standardized mortality ratio [SMR] 160; 95% confidence interval [CI] 102–251) was reported for a group of 6,153 workers with reported occupational exposure to trichloroethylene compared to a referent group of workers not exposed to any chemical (Blair et al. 1998). The follow-up period was 1952–1990 and the trichloroethylene-exposed workers were likely exposed to other chemicals as well. Asthma-related symptoms and lung function decrements were

Table 3-1 Levels of Significant Exposure to Trichloroethylene - Inhalation

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (Sprague-Dawley)	4 hr				12500 M (LC50)	Siegel et al. 1971	
2	Mouse (Albino)	4 hr				6400 (2/10 deaths)	Kylin et al. 1962	
Systemic								
3	Human	4 hr	Hemato	95 M			Konietzko and Reill 1980	
			Hepatic	95 M				
4	Human	5 d 7 hr/d	Hemato	200			Stewart et al. 1970	
			Hepatic	200				
			Ocular		200 (eye irritation)			
5	Human	2.5 hr	Cardio	200 M			Windemuller and Ettema 1978	
6	Rat (Fischer- 344)	6 hr	Renal		1000 M (increased urinary gamma-glutamyl transpeptidase, glucose, protein, serum urea nitrogen, decreased uptake of p-aminohippurate by renal cortical slices)		Chakrabarti and Tuchweber 1988	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
7	Rat (Wistar)	1 or 2 wk 5 d/wk 4 h/d	Resp		376 M (nasal irritation during exposure)		Kumar et al. 2002a	
			Ocular		376 M (ocular irritation during exposure)			
8	Rat (Alpk: APfSD)	6 hr	Resp		500 F (reduction of aldrin epoxidase and cytochrome C reductase activity)		Odum et al. 1992	
9	Rat (CD-1)	2 wk 5 d/wk 6 hr/d	Bd Wt	1000 M			Xu et al. 2004	
10	Mouse (CD-1)	6 hr	Resp	20 F	100 F (vacuolization of Clara cells, reduction of P-450 activity)		Odum et al. 1992	
11	Mouse (CD-1)	2 wk 5 d/wk 6 hr/d	Resp		450 F (vacuolization of Clara cells, reduction of P-450 activity)		Odum et al. 1992	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
12	Mouse (Hybrid)	7 d 8 h/d	Hepatic		1000 M (increased liver weight, minimal hepatocellular necrosis)		Ramdhan et al. 2008	
13	Mouse (B6C3F1)	30 min	Resp		500 M (vacuolization and dilation of endoplasmic reticulum in Clara cells)		Villaschi et al. 1991	
14	Dog (Beagle)	10 min	Cardio	5000 M		10000 M (7/12 ventricular fibrillation after epinephrine challenge, 1/12 cardiac arrest)	Reinhardt et al. 1973	
Immuno/ Lymphoret								
15	Mouse (CD-1)	3 hr		5 F	10 F (increased susceptibility to Streptococcus zooepidemicus)		Aranyi et al. 1986	
Neurological								
16	Human	2.5 hr		300 M			Ettema et al. 1975	
17	Human	~1 hr				3000 M (unconsciousness)	Longley and Jones 1963	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
18	Human	5 d 7 hr/d			200 (headache, fatigue, drowsiness)		Stewart et al. 1970	
19	Human	2 hr		300 M		1000 M (decreased depth perception and motor skills)	Vernon and Ferguson 1969	
20	Human	2.5 hr		200 M			Windemuller and Ettema 1978	
21	Rat (Wistar)	8 hr			3000 (lethargy)	4800 (anesthesia)	Adams et al. 1951	
22	Rat (Wistar)	3 d 8 hr/d or 4 hr/d		300 M	1000 M (decreased wakefulness, decreased postexposure heart rate)	3000 M (occasional seizures, postexposure arrhythmia)	Arito et al. 1993	
23	Rat (Long- Evans)	5 d 6 hr/d		2000 M		4000 M (postexposure mid-frequency hearing loss, sedation)	Crofton and Zhao 1993	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
24	Rat (Long- Evans)	Once 6 hr		4000 M	6000 M (14 dB increase in auditory threshold to 16 kHz)		Crofton and Zhao 1997	
25	Rat (Long- Evans)	5 d 6 hr/d		2400 M	3200 M (21 dB increase in auditory threshold for 16 kHz tone)		Crofton and Zhao 1997	
26	Rat (CFE)	10 d 5 d/wk 4 hr/d		1568 F		4380 F (ataxia)	Goldberg et al. 1964b	
27	Rat (NS)	6 hr		400 M	800 M (impaired swimming performance both with and without a load)		Grandjean 1963	
28	Rat (Wistar)	4 hr			250 M (decreased shock avoidance and Skinner box lever press)		Kishi et al. 1993	
29	Rat (pigmented)	1 hr			2754 (impaired oculomotor control)		Niklasson et al. 1993	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
30	Rat (Sprague-Dawley)	4 d 6 hr/d			200 M (decreased brain RNA, hyperactivity)		Savolainen et al. 1977	
Reproductive								
31	Rat (Wistar)	2 wk 5 d/wk 4 hr/d			376 M (increased sperm abnormalities, decreased reproductive success)		Kumar et al. 2000b	
32	Rat (CD-1)	2 wk 5 d/wk 6 hr/d			1000 M (decreased numbers of sperm attaching to eggs)		Xu et al. 2004	
33	Mouse (C57Bl/ 6J)	5 d 6 hr/d		500 M			Allen et al. 1994	
34	Mouse (CD-1)	5 d 7 hr/d			100 M (6% increase in abnormal sperm morphology)		Beliles et al. 1980	
35	Mouse (CD-1)	1 d; 1, 2, 3, or 4 wk 5 d/wk 5 hr/d			1000 M (degeneration of epididymal epithelium)		Kan et al. 2007	
36	Mouse (C57BL/ 6N)	5 d 4 hr/d		200 M	2000 M (1% increase in abnormal sperm morphology)		Land et al. 1981	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
Developmental								
37	Rat (Sprague-Dawley)	Gd 0-18 5 d/wk 7 hr/d		500			Beliles et al. 1980; Hardin et al. 1981	
38	Rat (Long- Evans)	Gd 0-20 7 d/wk 6 hr/d			1800 (decreased fetal weight, incomplete skeletal ossification)		Dorfmueller et al. 1979	
39	Rat (Sprague-Dawley)	Gd 6-15 7 hr/d		300			Schwetz et al. 1975	
40	Mouse (Swiss-Webster)	Gd 6-15 7 hr/d		300			Schwetz et al. 1975	
INTERMEDIATE EXPOSURE								
Systemic								
41	Monkey (Rhesus)	6 mo 5 d/wk 7 hr/d	Hepatic	400 M			Adams et al. 1951	
			Renal	400 M				
			Bd Wt	400 M				
42	Rat (Wistar)	6 mo 5 d/wk 7 hr/d	Hemato	400			Adams et al. 1951	
			Hepatic	400				
			Renal	400				
			Bd Wt	400				

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
43	Rat (Fischer- 344)	13 wk 5 d/wk 6 hr/d	Bd Wt	2500			Albee et al. 1993, 2006	
44	Rat (Sprague-Dawley)	Gd 6-20 6 hr/d	Hepatic	600 F			Carney et al. 2006	
			Renal	600 F				
			Bd Wt	600 F				
45	Rat (Wistar)	12 or 24 wk 5 d/wk 4 hr/d	Endocr			376 M (decreases in serum testosterone and testicular 17-beta-hydroxy steroid dehydrogenase levels)	Kumar et al. 2000a	
46	Rat (Wistar)	8, 12, or 24 wk 5 d/wk 4 hr/d	Hepatic		376 M (histopathologic liver lesions)		Kumar et al. 2001a	
47	Rat (Wistar)	12 or 24 wk 5 d/wk 4 hr/d	Bd Wt		376 M (22-29% decreased body weight gain)		Kumar et al. 2001b	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
48	Rat (Wistar)	28 or 90 d 5 d/wk 4 hr/d	Resp		376 M (histopathologic lung lesions)		Kumar et al. 2002b	
			Ocular		376 M (ocular irritation during exposure)			
49	Rat (Wistar)	10 wk 5 d/wk 8 hr/d	Hepatic	2000			Laib et al. 1979	
50	Rat (Wistar)	3 wk 5 d/wk 18 hr/d	Bd Wt		3000 (15% depressed body weight)		Muijser et al. 2000	
51	Rat (Sprague-Dawley)	90 d 24 hr/d	Resp	35			Prendergast et al. 1967	
			Cardio	35				
			Hemato	35				
			Hepatic	35				
			Renal	35				

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
52	Rat (Sprague-Dawley)	6 wk 5 d/wk 8 hr/d	Resp	712			Prendergast et al. 1967	
			Cardio	712				
			Hemato	712				
			Hepatic	712				
			Renal	712				
53	Rat (Sprague-Dawley)	4 wk 6 hr/d 5 d/wk	Hemato	1000 F			Woolhiser et al. 2006; Boverhof et al. 2013	
			Hepatic	300 F	1000 F (13% increased liver weight)			
			Renal	300 F	1000 F (17% increased kidney weight)			
			Bd Wt	1000 F				
54	Rat (CD-1)	6 wk 5 d/wk 6 hr/d	Bd Wt	1000 M			Xu et al. 2004	
55	Mouse (Hybrid)	8 wk 6 d/wk 4 hr/d	Bd Wt	2000 M			Kaneko et al. 2000	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
56	Mouse (NMRI)	30 d 24 hr/d	Hepatic	37 M 150 F	75 M (increased BuChE activity, liver weight)		Kjellstrand et al. 1983a	
					300 F (increased BuChE activity, liver weight)			
			Renal	37 M 75 F	75 M (39% increased kidney weight)			
					150 F (23% increased kidney weight)			
			Bd Wt	75 M 150 F	150 M (body weights 10% lower than controls)			
					300 F (body weights 16% lower than controls)			
57	Gn Pig (NS)	6 mo 5 d/wk 7 hr/d	Hepatic	400			Adams et al. 1951	
			Renal	400				
			Bd Wt	100 M	200 M (body weights 18% lower than controls)			

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
58	Rabbit (NS)	6 mo 5 d/wk 7 hr/d	Hepatic	400			Adams et al. 1951	
			Renal	400				
			Bd Wt	400				
Immuno/ Lymphoret								
59	Rat (Sprague-Dawley)	4 wk 6 hr/d 5 d/wk		300 F	1000 F (64% reduction in splenic anti-SRBC IgM response)		Woolhiser et al. 2006; Boverhof et al. 2013	
60	Mouse (Hybrid)	8 wk 6 d/wk 4 hr/d			500 M (decreased serum IgG)		Kaneko et al. 2000	
61	Mouse (B6C3F1)	30 wk (W)					Keil et al. 2009	MRL derived using HEC99 of 0.033 ppm from combined interspecies, intraspecies, and route-to-route extrapolation using PBPK model (see footnote b)
62	Mouse (NMRI)	30 d 24 hr/d		150	300 (41 and 24% decreased spleen weight in males and females, respectively)		Kjellstrand et al. 1983a	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
Neurological								
63	Rat (Fischer- 344)	13 wk 5 d/wk 6 hr/d		800	2500 (cochlear focal hair cell loss; frequency-specific hearing deficit, particularly at 16 kHz)		Albee et al. 1993, 2006	
64	Rat (JCL- Wistar)	6 wk 5 d/wk 8 hr/d			50 M (decreased wakefulness during exposure, decreased postexposure sleeping heart rate)	100 M (decreased postexposure wakefulness, decreased time-averaged postexposure heart rate)	Arito et al. 1994a	
65	Rat (NS)	44 wk 5 d/wk 8 hr/d			400 M (decreased swimming speed)		Battig and Grandjean 1963	
66	Rat (Long- Evans)	4 wk 5 d/wk 6 hr/d		2400 M	3200 M (27 dB increase in auditory threshold to 16 kHz tone)		Crofton and Zhao 1997	
67	Rat (Long- Evans)	13 wk 5 d/wk 6 hr/d		1600 M	2400 M (21 dB increase in auditory threshold to 16 kHz tone)		Crofton and Zhao 1997	
68	Rat (CFE)	30 d 5 d/wk 4 hr/d			125 M (decreased shock avoidance)		Goldberg et al. 1964a	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
69	Rat (Wistar)	3 wk 5 d/wk 18 hr/d			1500 (reduced acoustic startle response)		Jaspers et al. 1993	
70	Rat (Wistar)	18 wk 5 d/wk 16 hr/d		500 M	1000 M (increased latency in visual discrimination task)		Kulig 1987	
71	Rat (Wistar)	3 wk 5 d/wk 18 hr/d			3000 (significantly decreased auditory sensitivity to 4-20 kHz sound)		Muijser et al. 2000	
72	Rat (Long- Evans)	12 wk 6 d/wk 12 hr/d		1600 M	3200 M (depressed amplitude of auditory-evoked potentials)		Rebert et al. 1991	
73	Rat (Fischer- 344)	3 wk 6 d/wk 12 hr/d			2000 M (depressed amplitude of auditory-evoked potentials)		Rebert et al. 1991	
74	Rat (Wistar)	5 wk 5 d/wk 6 hr/d			100 M (reduced social behavior: exploration, escape, submission)		Silverman and Williams 1975	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
75	Rat (Wistar)	180 d 5 d/wk 4 h/d			376 M (increased spontaneous locomotor activity)		Waseem et al. 2001	
76	Rabbit (New Zealand)	12 wk 4 d/wk 4 hr/d			350 (altered amplitude of visual-evoked potentials)		Blain et al. 1992	
77	Rabbit (New Zealand albino)	12 wk 4 d/wk 4 h/d			350 M (decreased amplitude of oscillatory potentials and increased amplitude of a- and b-waves)		Blain et al. 1994	
78	Gerbil (Mongo- lian)	3 mo 24 hr/d			60 (astroglial hypertrophy)		Haglid et al. 1981	
Reproductive								
79	Rat (Wistar)	12 or 24 wk 5 d/wk 4 hr/d				376 M (decreased sperm concentration and motility, decreased serum testosterone, increased testicular cholesterol, decreased testicular glucose-6-phosphate dehydrogenase and 17-beta-hydroxy steroid dehydrogenase)	Kumar et al. 2000a	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
80	Rat (Wistar)	5-10 wk 5 d/wk 4 hr/d			376 M (increased incidence of sperm abnormalities, decreased reproductive success)		Kumar et al. 2000b	
81	Rat (Wistar)	12 or 24 wk 5 d/wk 4 hr/d				376 M (testicular atrophy, decreased sperm count, decreased sperm motility)	Kumar et al. 2001b	
82	Rat (CD-1)	6 wk 5 d/wk 6 hr/d			1000 M (decreased numbers of sperm that attached to eggs)		Xu et al. 2004	
83	Mouse (CD-1)	4 wk 5 d/wk 6 h/d			1000 M (epithelial cell damage in the epididymis)		Forkert et al. 2002	
84	Mouse (CD-1)	1 d; 1, 2, 3, or 4 wk 5 d/wk 5 hr/d				1000 M (serious degeneration of epididymal epithelium, damaged sperm after 4 weeks of exposures)	Kan et al. 2007	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
Developmental								
85	Rat (Sprague-Dawley)	Gd 6-20 6 hr/d		600			Carney et al. 2006	
86	Rat (Sprague-Dawley)	Throughout gestation (22 d)					Johnson et al. 2003	MRL derived using HEC99 of 0.0037 ppm from combined interspecies, intraspecies, and route-to-route extrapolation using PBPK model (see footnote b)
CHRONIC EXPOSURE								
Systemic								
87	Rat (Sprague-Dawley)	104 wk 5 d/wk 7 hr/d	Resp	600			Maltoni et al. 1988	
			Cardio	600				
			Gastro	600				
			Musc/skel	600				
			Hepatic	600				
			Renal	100 M 600 F	300 M (renal tubule meganucleocytosis)			
			Endocr	600				
			Dermal	600				
			Ocular	600				
			Bd Wt	600				

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
Cancer								
88	Rat (Sprague-Dawley)	104 wk 5 d/wk 7 hr/d				100 M (CEL: Leydig cell tumors)	Maltoni et al. 1986	
89	Mouse (ICR)	104 wk 5 d/wk 7 hr/d				150 F (CEL: lung adenomas and adenocarcinomas)	Fukuda et al. 1983	
90	Mouse (NMRI)	18 mo 5 d/wk 6 hr/d				100 F (CEL: increased lymphomas)	Henschler et al. 1980	
91	Mouse (B6C3F1)	78 wk 5 d/wk 7 hr/d				600 F (CEL: pulmonary tumors)	Maltoni et al. 1986	
92	Mouse (Swiss-Webster)	78 wk 5 d/wk 7 hr/d				600 M (CEL: pulmonary tumors and hepatomas)	Maltoni et al. 1986	

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

b Study results used as support for the EPA (2011e) preferred chronic RfC of 0.0004 ppm for trichloroethylene and the ATSDR chronic-duration and intermediate-duration inhalation MRLs for trichloroethylene. The preferred chronic RfC of EPA is based on results of two critical studies for which individual candidate chronic RfCs were derived: A candidate chronic RfC of 0.00033 ppm for decreased thymus weight in female mice exposed to trichloroethylene in the drinking water for 30 weeks (Keil et al. 2009), and a candidate chronic RfC of 0.00037 ppm for fetal heart malformations in rats exposed to trichloroethylene via the maternal drinking water during gestation (Johnson et al. 2003). Derivation of the EPA preferred chronic RfC included route-to-route extrapolation that employed PBPK modeling. Selected details regarding EPA's methodology for derivation of the preferred chronic RfC using results from the two critical studies are presented in Appendix A.

Bd Wt = body weight; BuChe = butyrylcholinesterase; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); dB = decibels; Endocr = endocrine; F = Female; Gastro = gastrointestinal; Gd = gestation day; Gn Pig = guinea pig; HEC99 = 99th percentile estimate of human equivalent concentration; Hemato = hematological; hr = hour(s); IgG = Immunoglobulin G; IgM = Immunoglobulin M; Immuno/Lymphoret = immunological/lymphoreticular; kHz = kiloHertz; LC50 = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; PBPK = physiologically-based pharmacokinetic; ppm = parts per million; Resp = respiratory; SRBC = sheep red blood cell; wk = week(s).

Figure 3-1 Levels of Significant Exposure to Trichloroethylene - Inhalation

Acute (≤14 days)

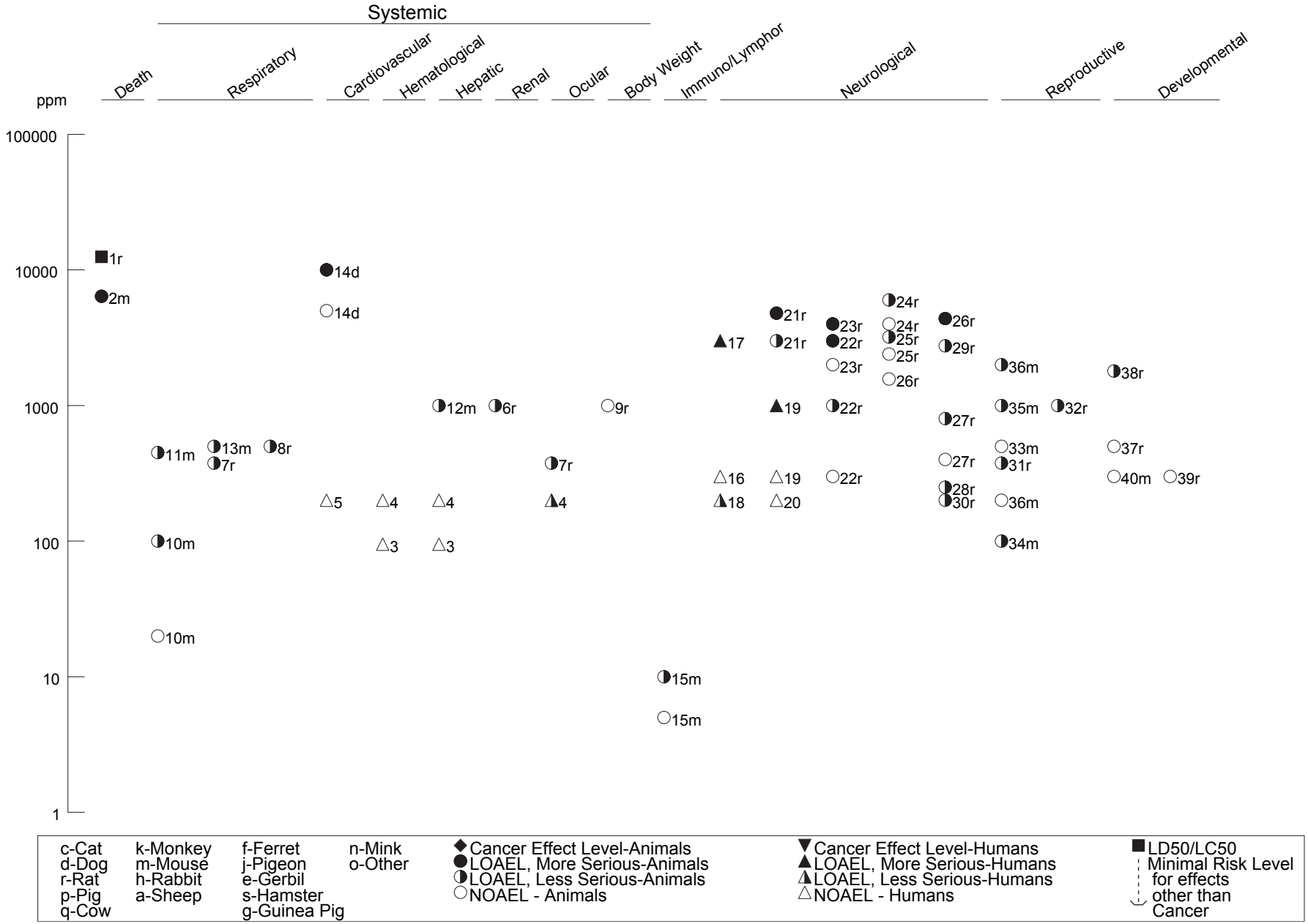


Figure 3-1 Levels of Significant Exposure to Trichloroethylene - Inhalation *(Continued)*

Intermediate (15-364 days)

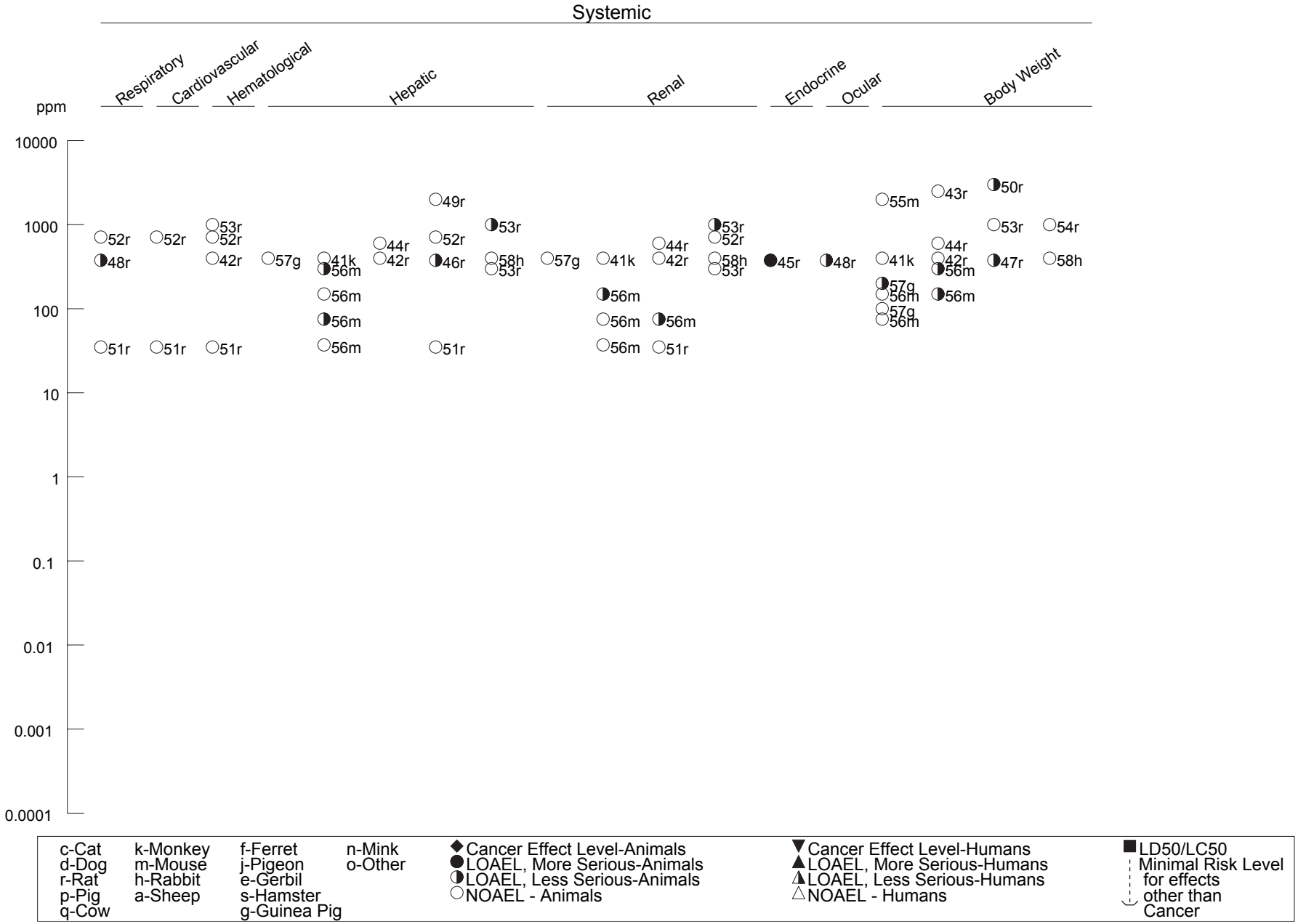


Figure 3-1 Levels of Significant Exposure to Trichloroethylene - Inhalation *(Continued)*

Intermediate (15-364 days)

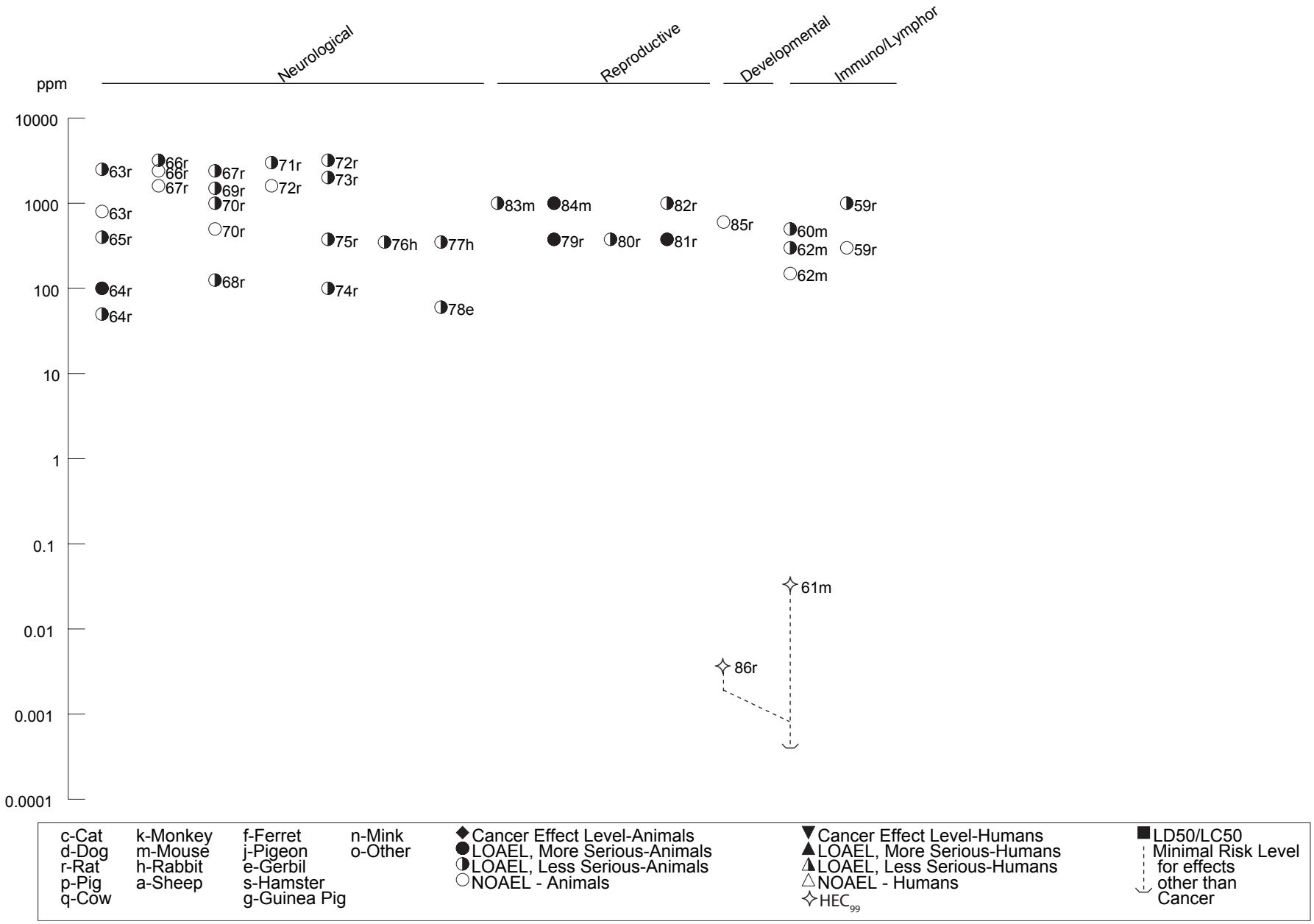
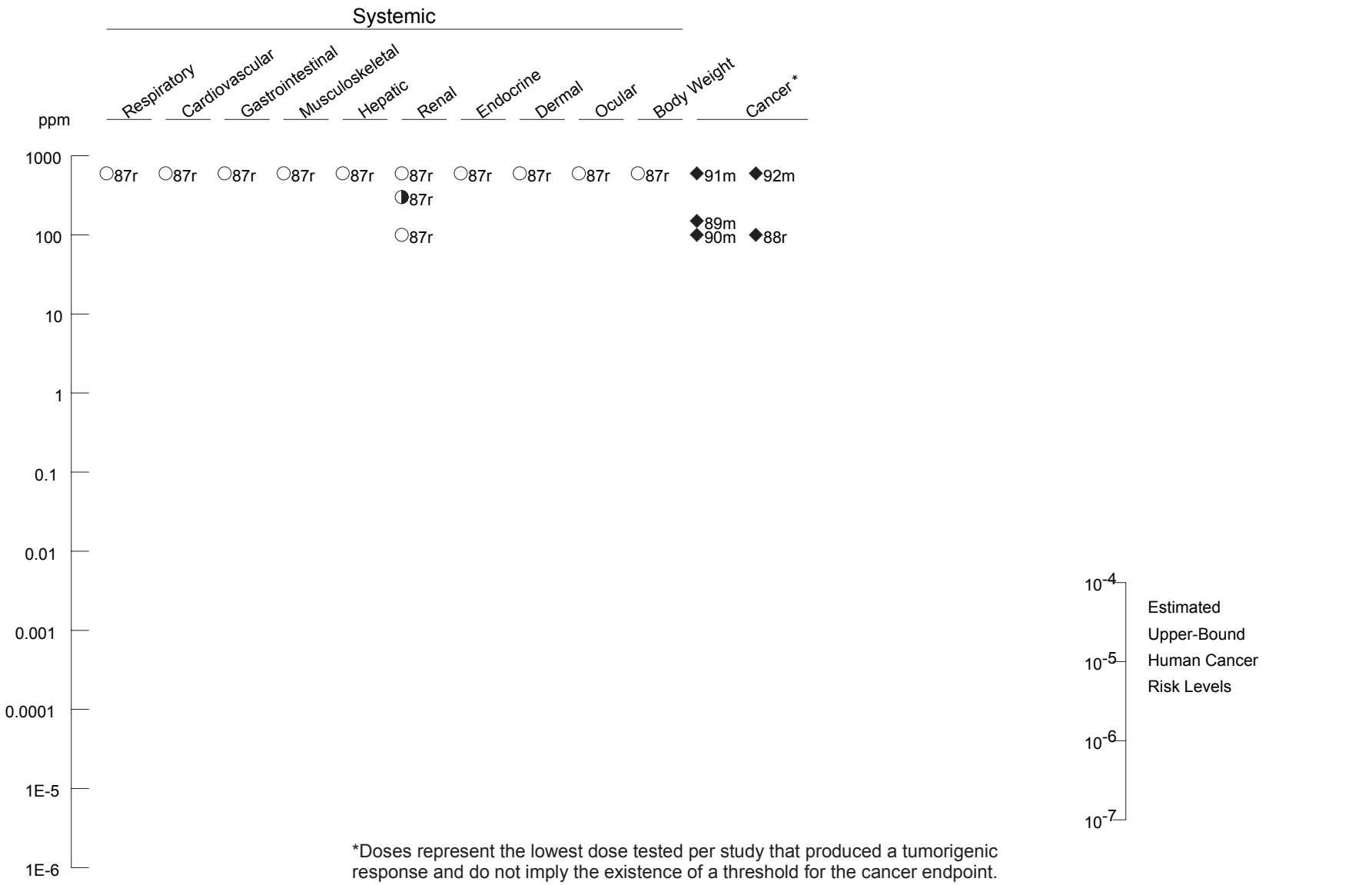


Figure 3-1 Levels of Significant Exposure to Trichloroethylene - Inhalation *(Continued)*

Chronic (≥365 days)



c-Cat	k-Monkey	f-Ferret	n-Mink	◆ Cancer Effect Level-Animals	▼ Cancer Effect Level-Humans	■ LD50/LC50
d-Dog	m-Mouse	j-Pigeon	o-Other	● LOAEL, More Serious-Animals	▲ LOAEL, More Serious-Humans	Minimal Risk Level for effects other than Cancer
r-Rat	h-Rabbit	e-Gerbil		◑ LOAEL, Less Serious-Animals	◭ LOAEL, Less Serious-Humans	
p-Pig	a-Sheep	s-Hamster		○ NOAEL - Animals	△ NOAEL - Humans	
q-Cow		g-Guinea Pig				

reported in studies of gun manufacturing workers exposed to solvents including trichloroethylene (Cakmak et al. 2004; Saygun et al. 2007), but the specific role of trichloroethylene in these symptoms could not be established.

Morphology of lung cells and activity of cytochrome P-450 (enzymes that metabolize xenobiotics) in the lungs have been studied in rats and mice exposed to trichloroethylene. Results of animal studies demonstrate that inhaled trichloroethylene can cause damage to Clara cells, which are nonciliated epithelial cells of the lung that produce a protective secretory protein, provide cytochrome P450 enzymes that assist in the metabolism of xenobiotics, and serve a function in regeneration of bronchiolar epithelium (see Reynolds and Malkinson 2010). A 30-minute inhalation exposure to 500 ppm resulted in vacuole formation and endoplasmic reticulum dilation specifically in Clara cells of the bronchial tree (Villaschi et al. 1991). Similar Clara cell-specific damage was observed in mice after a 6-hour exposure to 100 ppm trichloroethylene (Odum et al. 1992). A reduction in pulmonary cytochrome P-450 activity was also observed. After mice were exposed to 450 ppm trichloroethylene for 5 days, the Clara cell effects resolved, but after a 2-day break in the exposure, the effect returned (Odum et al. 1992). Rats, which have a lower abundance and different distribution of Clara cells than mice, exhibited no cell damage at 500 ppm, although P-450 activity was reduced following a 6-hour exposure (Odum et al. 1992). Kumar et al. (2002b) reported bronchiolitis and alveolitis in rats exposed to trichloroethylene vapors at 376 ppm, 4 hours/day, 5 days/week for 28 or 90 days; marked edema, presence of mononuclear cells, and unspecified emphysematous changes were noted after 90 days. These rats also exhibited signs of nasal irritation during exposures.

Cardiovascular Effects. Exposure of 15 male volunteers to 200 ppm trichloroethylene for 2.5 hours had no effect on heart rate or sinus rhythm (Windemuller and Ettema 1978). Electrocardiograms of workers exposed to trichloroethylene in the range of 38–172 ppm for periods ranging from <1 to >5 years did not show any adverse effects (El Ghawabi et al. 1973). A few case studies of persons who died following acute occupational exposure to trichloroethylene have revealed cardiac arrhythmias to be the apparent cause of death (Bell 1951; Kleinfeld and Tabershaw 1954; Smith 1966). In one case report, a woman had erratic heart action and abnormal electrocardiogram readings following exposure in the workplace (Milby 1968). Ventricular extrasystoles (also known as preventricular contractions or PVCs) were observed in a 34-year-old male worker during a workday in which personal monitoring revealed trichloroethylene levels between 50 and 100 ppm; the worker had no history of heart ailments and monitoring at the beginning of the workday and during a day without trichloroethylene exposure revealed no abnormalities (Konietzko and Elster 1973). In a cohort mortality of 14,457 aircraft maintenance

workers employed for at least 1 year between 1952 and 1956, a significant excess of death from ischaemic heart disease (SMR 108; 95% CI 103–113) was reported for a group of 6,153 workers with reported occupational exposure to trichloroethylene compared to a referent group of workers not exposed to any chemical (Blair et al. 1998). The follow-up period was 1952–1990; the trichloroethylene-exposed workers were likely exposed to other chemicals as well. A case-control study of 98 workers reported an increased risk of pulmonary veno-occlusive disease based on an adjusted odd ratio (OR, 95% CI) of 8.2 (1.4–49.4; p=0.022) (Montani et al. 2015). Although the risk estimate was adjusted for age, sex, and smoking history, exposure to other solvents was not considered as a potential confounder.

Inhalation of very high concentrations of trichloroethylene in incidents of poisonings (Dhuner et al. 1957; Gutch et al. 1965), or during its use as an anesthetic agent (Pembleton 1974; Thierstein et al. 1960), has been reported to lead to cardiac arrhythmias. The mechanism is unclear, but high doses of hydrocarbons such as trichloroethylene could act upon the heart to cause cardiac sensitization to catecholamines. This is supported by animal studies. For example, dogs (Reinhardt et al. 1973) and rabbits (White and Carlson 1979, 1981, 1982) exposed to very high concentrations of trichloroethylene (5,000 or 10,000 ppm, and 3,000 ppm, respectively) for ≤1 hour showed increased arrhythmias when injected intravenously with epinephrine. In animals, trichloroethylene itself, rather than its metabolites, is apparently responsible for the cardiac sensitization because chemicals that inhibit the metabolism of trichloroethylene increase its potency, while chemicals that enhance the metabolism of trichloroethylene decrease its potency (White and Carlson 1979, 1981).

No histopathological changes were observed in the hearts of squirrel monkeys, rats, guinea pigs, dogs, or rabbits exposed to 700 ppm trichloroethylene 8 hours/day, 5 days/week for 6 weeks, or to 35 ppm continuously for 6 weeks (Prendergast et al. 1967). Histopathological changes were also not observed in the hearts of rats exposed to 600 ppm trichloroethylene 7 hours/day, 5 days/week for 104 weeks (Maltoni et al. 1988).

Gastrointestinal Effects. Case reports indicate that acute inhalation exposure to trichloroethylene results in nausea and vomiting (Buxton and Hayward 1967; Clearfield 1970; David et al. 1989; DeFalque 1961; Gutch et al. 1965; Milby 1968). Anorexia, nausea, and vomiting have also been reported as chronic effects of occupational exposure to trichloroethylene (El Ghawabi et al. 1973). The exposure levels were not measured. Anorexia and vomiting were reported in a woman chronically exposed to occupational levels between 40 and 800 ppm (Schattner and Malnick 1990). Trichloroethylene-induced effects on the autonomic nervous system may contribute to these effects (Grandjean et al. 1955). Cases of pneumatosis

cystoides intestinalis (a rare condition characterized by gas-filled cysts in the submucosa of the small intestine) seen in Japanese lens cleaners and polishers were attributed to trichloroethylene exposure in the workplace (Nakajima et al. 1990a).

Histopathological changes in the gastrointestinal tract were not observed in rats exposed to 600 ppm trichloroethylene 7 hours/day, 5 days/week for 104 weeks (Maltoni et al. 1988).

Hematological Effects. There are limited data on hematological effects of trichloroethylene in humans. A study of humans exposed to 200 ppm trichloroethylene for a short period (7 hours/day for 1 or 5 days) revealed no adverse effects on blood cell counts or sedimentation rates (Stewart et al. 1970). Blood cell counts were also not affected in volunteers exposed to 1,000 ppm trichloroethylene for 2 hours (Vernon and Ferguson 1969). Volunteers inhaling trichloroethylene vapor at 95 ppm for 4 hours showed only an increase in neutrophil enzyme levels (alkaline and acid phosphatases, naphthol-AS-D esterase) (Konietzko and Reill 1980). The toxicological significance of this effect is unknown, however, because enzyme level changes may merely be the result of the nonspecific stimulation of metabolizing enzymes. No effects on hemoglobin levels or red blood cell counts were observed in workers exposed to trichloroethylene in the range of 38–172 ppm for periods ranging from <1–>5 years (El Ghawabi et al. 1973).

Various minor hematological effects have been noted in animals. Rats exposed to 50–800 ppm of trichloroethylene continuously for 48 or 240 hours showed time- and dose-related depression of delta-aminolevulinate dehydratase activity in liver, bone marrow, and erythrocytes (Fujita et al. 1984; Koizumi et al. 1984). Related effects included increased delta-aminolevulinic acid (ALA) synthetase activity, reduced heme saturation of tryptophan pyrrolase and reduced cytochrome P-450 levels in the liver, and increased urinary excretion of ALA and coproporphyrin. Since hemoglobin concentration in erythrocytes did not change, these changes are not considered to be adverse. Dogs exposed to 200 ppm trichloroethylene for 1 hour by tracheal intubation exhibited decreased leukocyte counts (Hobara et al. 1984). No effects on hematology examinations were noted in squirrel monkeys, rats, guinea pigs, dogs, or rabbits exposed to 700 ppm trichloroethylene 8 hours/day, 5 days/week for 6 weeks, or to 35 ppm continuously for 6 weeks (Prendergast et al. 1967). Hematological effects were also not observed in rats exposed intermittently for intermediate durations at 1,000 ppm (Boverhof et al. 2013), 400 ppm (Adams et al. 1951), or 55 ppm (Kimmerle and Eben 1973a).

Musculoskeletal Effects. Muscle necrosis was reported within 3 hours following the collapse of a 36-year-old female factory worker who was overcome by trichloroethylene vapors used to degrease metal; the exposure included a dermal component (Thorburn et al. 2004). Trichloroethylene exposure can cause nervous system effects that result in secondary effects on muscle strength, especially in the face (Leandri et al. 1995). See Section 3.2.1.4 for further discussion of nervous system effects following trichloroethylene exposure.

Histopathological changes in the thigh muscle were not observed in rats exposed to 600 ppm trichloroethylene 7 hours/day, 5 days/week for 104 weeks (Maltoni et al. 1988).

Hepatic Effects. There is some evidence for trichloroethylene-induced hepatotoxic effects in humans. However, much of this information is limited by the fact that the exposure levels associated with these effects were usually not reported, and the individuals may have been exposed to other substances as well. Reports that support the liver as a target of trichloroethylene toxicity are summarized below.

Multiple case reports implicate trichloroethylene as a liver toxicant. A 37-year-old male with occupational exposure to trichloroethylene and a reportedly unprotected high-level acute exposure to trichloroethylene vapors during the preparation of a solvent mixture presented to a hospital in a jaundiced condition and died several weeks later; acute massive liver necrosis was noted at autopsy (Joron et al. 1955). Acute hepatic necrosis was also seen in a degreaser who died after being exposed to trichloroethylene for at least 6 weeks (Priest and Horn 1965). Two case studies of people hospitalized after intentional acute inhalation of very high concentrations of trichloroethylene showed liver damage at autopsy in one and hepatocyte degeneration revealed by liver biopsy in the other (Clearfield 1970). In contrast, James (1963) saw only small foci of fatty degeneration in the liver of a man who had intentionally inhaled trichloroethylene during a 10-year span. Other case studies reported liver effects such as jaundice, hepatomegaly, hepatosplenomegaly, hepatitis, and liver failure in patients with occupational or nonoccupational exposure to trichloroethylene (Anagnostopoulos et al. 2004; Caprioli et al. 2001; Chae et al. 1999, 2003; Chittasobhaktra et al. 1997; Goon et al. 2001; Ha et al. 2009; Huang et al. 2006; Jung et al. 2012; Kamijima et al. 2007; Nakayama et al. 1988; Pantucharoensri et al. 2004; Thiele et al. 1982; Xu et al. 2009).

There are reports of fatal hepatic failure in eclamptic pregnant women following trichloroethylene anesthesia (DeFalque 1961). Exposure concentrations and durations were not provided. Women who were exposed to 1,000 ppm of trichloroethylene during surgery for Caesarean sections exhibited no

evidence of liver toxicity (Crawford and Davies 1975). Although liver function tests were not completed, 250 neurosurgery patients, anesthetized with trichloroethylene for 3–5-hour periods, showed no evidence of liver damage during the postoperative period (Brittain 1948). Pembleton (1974) reviewed data on 550 patients who had undergone trichloroethylene anesthesia for a variety of operative procedures. For 100 of these patients, a number of pre- and postoperative liver function tests were reported. Four of 100 patients had a postoperative rise in serum glutamic-oxaloacetic transaminase (aspartate aminotransferase; AST), which returned to normal within 2 or 3 days. One patient had a doubling of the AST level, which also returned to normal by day 3. Other liver function tests evidently remained within normal ranges. A significant increase in the metabolism of the drug, paracetamol, was observed in patients anesthetized with trichloroethylene, indicating that determining the proper dosage in such cases may not be straightforward because of effects on liver function (Ray et al. 1993). Overall, the available data indicate that controlled trichloroethylene anesthesia produces minimal effects on the liver.

Other case reports indicate that exposure to trichloroethylene in the workplace can cause changes in blood and urine indices of liver function and possibly cause liver pathology (Graovac-Leposavic et al. 1964). Acute hepatitis developed in a woman occupationally exposed to between 40 and 800 ppm over a period of several years (Schattner and Malnick 1990). Changes in levels of serum liver enzymes (Nagaya et al. 1993; Rasmussen et al. 1993b; Xu et al. 2009) and bile acids (Driscoll et al. 1992; Neghab et al. 1997) among individuals exposed to trichloroethylene in the workplace were indicative of liver toxicity. A case report of four workers who had dermal reactions to trichloroethylene exposure showed no adverse liver function in three persons, but an enlarged liver in one worker (Bauer and Rabens 1974). Among 14 workers exposed to trichloroethylene at an unspecified concentration above the occupational standard, enlarged liver was observed in 3 workers, increased serum transaminase activity was observed in 9 workers, and liver biopsies of 13 workers revealed fatty acid deposition in 11 workers (Schuttmann 1970).

There was no clear evidence of liver effects within a group of 289 British workers who exhibited trichloroethylene-induced neurological effects; no information was provided regarding trichloroethylene exposure levels (McCarthy and Jones 1983). No significant association was found between occupational exposure to trichloroethylene and death from liver cirrhosis in multiple cohort mortality studies (ATSDR 2004; Blair et al. 1998; Boice et al. 1999, 2006; Garabrant et al. 1988; Morgan et al. 1998; Radican et al. 2008; Ritz 1999).

Liver function tests were normal in volunteers exposed for 5 days to 95 ppm for 4 hours/day (Konietzko and Reill 1980) or 200 ppm for 7 hours/day (Stewart et al. 1970).

Inhalation of trichloroethylene for acute or intermediate periods can cause liver enlargement in laboratory animals. This effect is usually reversible when exposure ceases. Histological changes were observed in some studies but not in others. Liver weight and plasma butyrylcholinesterase (BuChE) activity were increased in various strains of mice exposed to 37–300 ppm continuously for 30 days (Kjellstrand et al. 1983a, 1983b). In this study, histological examinations revealed misshapen, enlarged, and vacuolated hepatocytes. After 4 months of postexposure recovery, liver weight and serum BuChE activity had returned to normal; the only remaining histopathological effect was that of hepatocyte enlargement. Male mice were more sensitive to the hepatic effects than female mice. In male mice, the liver effects were observed at 75 ppm with a NOAEL of 37 ppm, while in female mice, the liver effects occurred at 300 ppm with a NOAEL of 150 ppm. The study authors suggested that the effects were not toxicologically significant. Another study in rats reported a dose-effect relationship between trichloroethylene exposure concentrations (50–800 ppm) or duration and inhibition of liver ALA dehydratase activity following continuous 48-hour and 10-day exposures. However, the toxicological significance of these effects is not known because the changes occurred in the absence of gross liver injury (Koizumi et al. 1984). In related studies, mice, rats, and gerbils were exposed continuously for up to 30 days to 150 ppm of trichloroethylene (Kjellstrand et al. 1981). The study authors reported increased relative liver weight in all species and treatment groups, but the effect was more pronounced in the mice (60–80% enlargement) than the rats or gerbils (20–30%). Examination of mice 5 and 30 days after cessation of treatment indicated that the increase in liver weight had decreased. Limitations of this study include lack of histopathologic evaluation of liver tissue and limitations in methodology used to record and evaluate body weight data. Kumar et al. (2001a) reported significantly increased liver weight and hepatocellular fatty and necrotic liver lesions in male rats exposed to trichloroethylene vapors at 376 ppm for 4 hours/day 5 days/week for 8, 12, or 24 weeks; the liver lesions became progressively more severe with duration, but quantitative data were not included in the study report. Ramdhan et al. (2008) reported concentration-related increased liver weight (43–64% higher than controls) and minimal to moderate hepatocellular necrosis in male wild type (CYP2E1+/+) mice exposed to trichloroethylene vapors at 1,000 or 2,000 ppm for 8 hours/day on 7 consecutive days; similarly-exposed CYP2E1-null mice exhibited no signs of exposure-related liver effects, indicating that the liver effects in the wild type mice are associated with CYP2E1-mediated metabolism. In a study designed to assess the role of human and mouse PPARα in trichloroethylene-induced liver effects, male wild-type (mPPARα), PPARα-null, and humanized PPARα (hPPARα) mice on Sv/129 background were exposed to trichloroethylene by

inhalation at 0, 1,000, or 2,000 ppm 8 hours/day for 7 days (Ramdhan et al. 2010). Trichloroethylene-exposed mice of each cell line exhibited increased plasma alanine aminotransferase (ALT) and AST activities, hepatocellular inflammation and necrosis, and elevated nuclear factor-kappa B p52 mRNA and protein. Hepatic lipid accumulation, increased expression of triglyceride-synthesizing enzymes, diacyl-glycerol acyltransferases, and PPARγ were observed in the PPARα-null and hPPARα mice, but not the mPPARα mice. Rats, guinea pigs, rabbits, dogs, and squirrel monkeys were exposed to 35 ppm trichloroethylene continuously for 90 days or to 712 ppm 8 hours/day, 5 days/week for 6 weeks. Although liver weight was not determined, gross and histopathological examinations of the liver were unremarkable (Prendergast et al. 1967). In rats exposed to 55 ppm trichloroethylene intermittently (8 hours/day, 5 days/week) for 14 weeks, increased liver weight was observed, but there were no effects on hepatic function or gross appearance of the liver (Kimmerle and Eben 1973a). Histology of the liver was not examined in this study. Rats, guinea pigs, rabbits, and Rhesus monkeys exposed intermittently to 400 ppm of trichloroethylene for 6 months (173 exposures in 243 days) exhibited increased liver weight, but there were no gross or histological hepatic alterations (Adams et al. 1951). An increase in nucleoside-5-triphosphatase-deficient foci (considered to be preneoplastic) was not observed in the livers of newborn rats exposed to 2,000 ppm trichloroethylene 8 hours/day, 5 days/week for 10 weeks (Laib et al. 1979). No histopathological changes were observed in the livers of rats exposed to 300 ppm trichloroethylene 7 hours/day, 5 days/week for 104 weeks (Maltoni et al. 1988). Only slightly (but statistically significant) increased liver weight was observed in female rats intermittently exposed to trichloroethylene vapors at 1,000 ppm for 4 weeks (Boverhof et al. 2013) or pregnant rats exposed for 6 hours/day on GDs 6–20 at 600 ppm (Carney et al. 2006); histopathologic liver examinations were not performed.

Renal Effects. Trichloroethylene may have effects in the kidney; however, studies in humans are limited by having poor or no exposure data and by concomitant exposure to other chemicals. There was no evidence of kidney damage in 250 neurosurgery patients who underwent prolonged trichloroethylene anesthesia (Brittain 1948), nor in 405 women who had Caesarean sections and were subjected to trichloroethylene anesthesia (Crawford and Davies 1975).

There are few reports of renal dysfunction in workers exposed to trichloroethylene. One case report indicates that a man using trichloroethylene in de-inking operations (for 8 hours) developed acute renal failure due to acute allergic interstitial nephritis with secondary tubular necrosis (David et al. 1989). Acute renal failure was reported in one man acutely exposed to trichloroethylene, although the man was also known to have a history of excessive abuse of alcohol (Gutch et al. 1965). Proteinuria was reported in a man who intentionally inhaled a spot-remover containing trichloroethylene and petroleum solvents

(Clearfield 1970). Renal toxicity, as indicated by changes in urinary proteins and N-acetyl-β-d-glucos-aminidase (NAG) (Brogren et al. 1986; Brüning et al. 1999; Carrieri et al. 2007; Nagaya et al. 1989b; Selden et al. 1993), have been found in workers exposed to trichloroethylene and other chemicals in the workplace. The increase in these markers of kidney effects suggests that trichloroethylene may affect both glomeruli and renal tubules. In a study of 80 trichloroethylene-exposed workers and 45 unexposed workers within several factories in China, the exposed workers exhibited urinary kidney molecule-1 (KIM-1) levels that were 50% higher than control levels (p=0.01) (Vermeulen et al. 2012). KIM-1 is a transmembrane protein expressed in dedifferentiated proximal renal tubular epithelial cells within damaged regions (Huo et al. 2010) and has been shown to be a more sensitive biomarker of renal damage than traditional biomarkers of renal injury (serum creatinine and blood urea nitrogen [BUN]) in rat studies (Vaidya et al. 2010). Personal trichloroethylene exposure measurements taken during a 2-week period prior to the collection of urine indicated a mean trichloroethylene exposure level of 22.2 ppm; measurements from 96% of the exposed workers were below the OSHA 8-hour TWA permissible exposure limit of 100 ppm. Evaluation of other markers of kidney toxicity (alpha-GST, Pi-GST, vascular endothelial growth factor, NAG, and creatinine) resulted in p-values of 0.98, 0.09, 0.99, 0.94, and 0.27, respectively. The study authors indicated that the mean Pi-GST level among the trichloroethylene-exposed workers was indicative of a borderline statistically significant effect (Vermeulen et al. 2012).

Green et al. (2004) assessed renal dysfunction in a cross-sectional study of 70 workers exposed to trichloroethylene and 54 age- and sex-matched individuals without trichloroethylene exposure by measuring urinary levels of NAG and albumin. Urinary trichloroacetic acid (TCA) concentration was used to estimate trichloroethylene exposure level (mean 32 ppm; range 0.5–252 ppm). Urinary levels of NAG and albumin were significantly higher in the trichloroethylene-exposed workers, although neither parameter was correlated with exposure level or duration. Evidence of increased urinary formate, methylmalonate, and glutathione S-transferase α activity in the exposed workers, although within the control range, indicate that higher exposure levels would likely have resulted in more clear evidence of trichloroethylene-induced kidney effects.

Radican et al. (2006) performed a retrospective cohort study of end-stage renal disease in aircraft workers exposed to trichloroethylene and other hydrocarbons by matching an occupational database to the U.S. Renal Data System and examining the all-cause end-stage renal disease using multivariate Cox regression. The evaluation spanned the years 1973–2002; the time period during which exposure occurred was not reported. Among 6,532 aircraft workers with reported trichloroethylene exposure and a group of 3,327 referents with no reported chemical exposure, an approximately 2-fold increased risk of

end-stage renal disease was observed for the trichloroethylene-exposed aircraft workers (hazard ratio [HR] 1.92; 95% CI 1.03–3.59) for the period of 1973–1999. For the period of 1973–2000, increased risk of end-stage renal disease in the trichloroethylene-exposed workers was noted among those workers with 5–25 unit-years of exposure (HR 2.48; 95% CI 1.20–5.15), workers with indirect low/intermittent exposures (HR 2.47; 95% CI 1.17–5.19), and workers with indirect peak/infrequent exposures (HR 3.66; 95% CI 1.25–10.74). For workers exposed for periods <5 years or >25 years, HRs were 1.73 (95% CI 0.86–3.48) and 1.65 (95% CI 0.82–3.35), respectively. Taken together, the results provide evidence of trichloroethylene-induced renal effects.

Jacob et al. (2007) evaluated a possible association between progression of primary glomerulonephritis to end-stage renal disease among 269 patients and exposure to trichloroethylene based on self-reported job description. For those patients considered to have been occupationally exposed to any level of trichloroethylene (n=20), six patients exhibited progression to end-stage renal disease (HR 2.5; 95% CI 0.9–6.5). Among 10 of the patients with assumed high-level exposure, an HR of 2.7 (95% CI 0.7–10.1) was reported. This study is limited by the lack of measured trichloroethylene levels and the small numbers of trichloroethylene-exposed participants. No evidence was found for associations between trichloroethylene and noncancer kidney effects in other cohort studies (Boice et al. 2006; Lipworth et al. 2011; Silver et al. 2014).

Exposure of rats to extremely high levels (≥1,000 ppm) for periods of <1 day led to the dysfunction of the tubular and glomerular regions of the nephron, as indicated by increases in urinary glucose, proteins, glucosaminidase, gamma glutamyl transpeptidase, and serum urea nitrogen (Chakrabarti and Tuchweber 1988). Mensing et al. (2002) reported increased urinary levels of high-molecular-weight proteins and albumin (biomarkers of glomerular damage) and NAG and low-molecular-weight proteins (biomarkers of proximal tubule damage) in male rats exposed to trichloroethylene vapors at 500 ppm, 6 hours/day, 5 days/week for 6 months. Histopathologic examinations of the kidneys revealed perivascular, interstitial inflammation and glomerulonephritis. Increased kidney weight has been found in rats, mice, and gerbils repeatedly or continuously exposed to trichloroethylene vapors in the range of 50–1,000 ppm for 4–14 weeks (Boverhof et al. 2013; Kimmerle and Eben 1973a; Kjellstrand et al. 1981, 1983a, 1983b). However, the toxicological significance of the increased organ weight is uncertain because no histopathological changes were observed and no functional tests were performed. Adams et al. (1951) reported significantly increased kidney weight in rats and rabbits repeatedly exposed to trichloroethylene vapors at 3,000 ppm for 36 days and in rats exposed at 400 ppm for as long as 243 days; however, there was no histopathological evidence of exposure-related renal effect. Prendergast et al. (1967) found no

histopathological evidence of trichloroethylene-induced renal effects in groups of rats, guinea pigs, rabbits, dogs, and squirrel monkeys repeatedly exposed by inhalation for 6 weeks at a concentration of 3,825 mg/m^3 (688 ppm); organ weight data were not provided in the study report. Male rats, but not female rats, that were exposed to 300 ppm trichloroethylene in a chronic study showed renal tubular megalonucleocytosis (Maltoni et al. 1986, 1988). The study authors considered that this histopathological change might be a precancerous lesion; however, no kidney tumors were observed. The serious shortcomings of these chronic studies are discussed in Section 3.2.1.7.

Endocrine Effects. In occupational studies of men who used trichloroethylene to degrease electronic equipment, increasing years of exposure to trichloroethylene were associated with increased serum dehydroepiandrosterone sulphate (a metabolite of the endogenous steroid hormone dehydroepiandrosterone) and decreases in serum levels of testosterone, follicle-stimulating hormone, and sex-hormone binding globulin (Chia et al. 1997; Goh et al. 1998). Serum androstenedione, cortisol, and aldosterone levels were in normal ranges. In the study of Goh et al. (1998), the serum insulin level among those workers with <2 years of exposure (40.8 mLU/L) was notably higher than that of unexposed controls (9.6 mLU/L); however, insulin levels returned to normal among workers exposed for longer periods. There is suggestive evidence of an association between exposure to trichloroethylene and menstrual cycle disturbances (including amenorrhea) (Bardodej and Vyskocil 1956; Sagawa et al. 1973; Zielinski 1973).

No histopathological changes in the pituitary gland, adrenal glands, or pancreas were observed in rats exposed to 600 ppm trichloroethylene 7 hours/day, 5 days/week for 104 weeks (Maltoni et al. 1988). Significantly decreased serum testosterone (31–48% less than that of controls) and decreased testicular 17β-hydroxy steroid dehydrogenase were noted in rats exposed to trichloroethylene vapors at 376 ppm, 4 hours/day, 5 days/week for 12 or 24 weeks (Kumar et al. 2000a).

Dermal Effects. Dermal effects of trichloroethylene exposure in humans are usually the consequence of direct skin contact with concentrated solutions, but occupational exposure also involves vapor contact. Adverse effects have not been reported from exposure to dilute aqueous solutions. Humans who were experimentally exposed to 200 ppm of trichloroethylene vapor for 7 hours experienced dry throats (40% of the subjects), beginning after 30 minutes (Stewart et al. 1970). The subjects experiencing these symptoms did not experience them when exposed in the same manner on 5 other consecutive days. These effects are presumed to be due to direct contact with the vapor.

Generalized skin disorders, manifested as irritation and rashes, have resulted from occupational exposure to trichloroethylene (Bauer and Rabens 1974; Chittasobhaktra et al. 1997; El Ghawabi et al. 1973; Huang et al. 2006; Kamijima et al. 2007; Pantucharoensri et al. 2004; Xu et al. 2009). An exfoliative dermatitis (Goh and Ng 1988), scleroderma (Czirjak et al. 1993), and eosinophilic fasciitis (Hayashi et al. 2000), thought to have immune components, have been reported in persons occupationally exposed to trichloroethylene. Refer to Section 3.2.1.3 for information regarding occupational exposure to trichloroethylene and immunological responses.

Histopathological changes in the skin were not observed in rats exposed to 600 ppm trichloroethylene 7 hours/day, 5 days/week for 104 weeks (Maltoni et al. 1988).

Ocular Effects. Humans who were experimentally exposed to 200 ppm of trichloroethylene vapor for 7 hours experienced mild eye irritation (20% of the subjects), beginning after 30 minutes (Stewart et al. 1970). The subjects experiencing these symptoms did not again experience them when exposed in the same manner on 5 other consecutive days. Itchy, watery eyes (Bauer and Rabens 1974; El Ghawabi et al. 1973) and inflamed eyes (Schattner and Malnick 1990) have also been reported following contact with the vapor.

Ocular irritation was observed during exposures of rats to trichloroethylene vapors at 376 ppm (Kumar et al. 2002a, 2002b). Histopathological changes in the eyes were not reported in rats exposed to 600 ppm trichloroethylene 7 hours/day, 5 days/week for 104 weeks (Maltoni et al. 1988).

Body Weight Effects. Body weight loss has been reported in humans occupationally exposed to trichloroethylene for intermediate or chronic durations at concentrations resulting in neurological effects (Mitchell and Parsons-Smith 1969; Schattner and Malnick 1990).

Exposure to trichloroethylene vapors resulted in depressed body weight or body weight gain in some studies of laboratory animals. Kumar et al. (2001b) reported >20% depressed body weight gain in male rats exposed to trichloroethylene vapors at 376 ppm, 4 hours/day, 5 days/week for 12 or 24 weeks. In other rat studies, no body weight effects were observed following intermittent or continuous exposure to trichloroethylene vapors at exposure levels in the range of 400–2,500 ppm for 2 weeks to as much as 2 years (Adams et al. 1951; Albee et al. 2006; Boverhof et al. 2013; Carney et al. 2006; Maltoni et al. 1988; Prendergast et al. 1967; Xu et al. 2004). In a group of male mice exposed to trichloroethylene continuously at 150 ppm for 30 days, mean body weight was 10% lower than that of controls (Kjellstrand

et al. 1983a). There was no effect on body weight of similarly-exposed females; however, the next higher exposure level (300 ppm) resulted in 18 and 16% lower mean body weight in males and females, respectively. In another mouse study (Kaneko et al. 2000), exposure of males to trichloroethylene at 2,000 ppm, 4 hours/day, 6 days/week for 8 weeks had no effect on body weight. Male guinea pigs exposed to 200 ppm trichloroethylene 7 hours/day, 5 days/week for 6 months exhibited 18% lower body weight than controls; however, there was no effect on female guinea pigs similarly exposed to 400 ppm (Adams et al. 1951). Body weight was not affected in Rhesus monkeys or rabbits exposed to 400 ppm 7 hours/day, 5 days/week for 6 months (Adams et al. 1951).

3.2.1.3 Immunological and Lymphoreticular Effects

Occupational exposure to trichloroethylene may involve both inhalation and dermal routes. Results of numerous case reports indicate that people can develop hypersensitivity-type reactions to trichloroethylene (Chae et al. 1999, 2003; Conde-Salazar et al. 1983; Czirjak et al. 1993; Goh and Ng 1988; Goon et al. 2001; Ha et al. 2009; Hayashi et al. 2000; Jung et al. 2012; Kamijima et al. 2007, 2008; Nakayama et al. 1988; Phoon et al. 1984; Raşcu et al. 2003; Waller et al. 1994; Xu et al. 2009) that may involve skin, mucous membranes, and the liver. Phoon et al. (1984) reported on five cases of individuals who developed generalized erythema and maculopapular lesions with exfoliation, conjunctivitis (corneal ulcers in one case), and liver dysfunction; all had been occupationally-exposed to trichloroethylene for 2–5 weeks. Although patch testing of one case about 6 months later provided negative results, it was suggested that adverse effects were the result of a hypersensitivity response to trichloroethylene because exposure levels were described as “not very high” and other workers in the same environments were not affected. Goon et al. (2001) reported a case in which a trichloroethylene-exposed worker presented with dermal lesions, irritation of mucous membrane, and liver dysfunction; it was suggested that the condition be named trichloroethylene hypersensitivity syndrome. Other investigators have reported similar cases (e.g., Chae et al. 2003; Ha et al. 2009; Jung et al. 2012). Dermal sensitivity was confirmed with patch testing in three cases (Conde-Salazar et al. 1983; Ha et al. 2009; Nakayama et al. 1988).

Iavicoli et al. (2005) reported alterations of the immune system, expressed as significantly altered serum levels of selected cytokines (increased interleukin-2 and interferon-γ and decreased interleukin-4), in a group of factory workers who were exposed to trichloroethylene at a mean workplace air concentration of 35 ± 14 mg/m^3 (6.3 ppm) for at least 3 years during degreasing processes. The exposed group was compared to a group of workers not directly involved in the degreasing process and a group of nonexposed office workers. Immune function was not tested in this study. Bassig et al. (2013) reported

significantly decreased serum interleukin-10 in a group of 71 workers exposed to trichloroethylene when compared to a group of 78 unexposed workers; the magnitude of the decrease was 70%. The magnitude was >60% among those workers exposed at levels <12 ppm. In another study that included a cohort of 80 trichloroethylene-exposed workers and 45 unexposed control workers, significantly decreased serum IgG and IgM levels were reported for the exposed workers (17.5 and 38%, respectively, lower than controls) (Zhang et al. 2013).

There is some evidence for an association between occupational exposure to trichloroethylene and the occurrence of scleroderma (systemic sclerosis, a chronic autoimmune disease primarily of the skin) (Diot et al. 2002; Garabrant et al. 2003; Nietert et al. 1998). A meta-analysis of these studies resulted in combined ORs of 2.5 (95% CI 1.1–5.4) for any exposure in men and 1.2 (95% CI 0.58–2.6) in women (Cooper et al. 2009; EPA 2011e). Increased risk of scleroderma may be easier to detect in trichloroethylene-exposed male workers than female workers because, within various populations, women are on average approximately 3 times more likely than men to develop scleroderma (Chifflot et al. 2008). Evaluation of a potential association between occupational exposure to trichloroethylene and the occurrence of scleroderma in a case-control study of 100 scleroderma patients and 300 controls resulted in a reported OR of 2.26 (95% CI 0.95–5.26) (Marie et al. 2014). Limiting the evaluation to those cases (n=8) and controls (n=7) with a high cumulative score for trichloroethylene exposure, the OR was 3.63 (95% CI 1.15–12.09).

Occupational exposure to trichloroethylene was associated with decreases in selected lymphocyte subsets among trichloroethylene-exposed workers (n=80) at factories in China that used trichloroethylene for cleaning a variety of materials and products; controls consisted of 96 unexposed age- and sex-matched workers from other industries (Hosgood et al. 2012; Lan et al. 2010). Full-shift personal air monitoring was performed to assess trichloroethylene exposure levels. The study authors noted significantly lower total numbers of lymphocytes, T cells, CD4+ T cells, CD8+ T cells, B cells, and natural killer (NK) cells among the trichloroethylene-exposed workers (Lan et al. 2010). When the trichloroethylene-exposed workers were categorized according to exposure level, those in the higher exposure category (≥12 ppm; mean 38 ppm) exhibited more marked decreases in total lymphocytes and lymphocyte subsets than those in the lower exposure category (<12 ppm; mean 5 ppm). Relative to unexposed controls, the trichloroethylene-exposed group of workers exhibited 8% decreased CD4+ naïve T cell count (p=0.056), 17% decreased CD8+ naïve T cell count (p=0.0002), and 20% decreased CD4+ effective memory T cell count (p=0.001) (Hosgood et al. 2012). These results suggest that trichloroethylene toxicity may include immunosuppression by depressing the capacity to respond to antigens. Analysis of serum concentrations

of IgG, IgM, and IgE from the 80 trichloroethylene-exposed workers and 45 of the unexposed controls revealed significantly ($p<0.01$) decreased IgG and IgM in the trichloroethylene-exposed workers (approximately 18 and 38%, respectively, lower than controls), but no significant effect on serum IgE (Zhang et al. 2013). Similar decreases in IgG and IgM were observed when controls were compared to those workers exposed to trichloroethylene levels either <12 or ≥12 ppm.

Some animal studies provide evidence for trichloroethylene-induced immunosuppression. A 64% reduction in splenic anti-SRBC IgM response was observed in female rats exposed to trichloroethylene vapors at 1,000 ppm, 6 hours/day, 5 days/week for 4 weeks; the NOAEL for immunological effects was 300 ppm (Boverhof et al. 2013). Kaneko et al. (2000) reported exposure concentration-related decreased serum IgG levels, liver inflammation, splenomegaly, and hyperplasia of lymphatic follicles in male mice of an autoimmune-prone strain repeatedly exposed to trichloroethylene at concentrations ≥500 ppm for 8 weeks. Male and female mice repeatedly exposed to trichloroethylene vapors at 300 ppm for 8 weeks exhibited significantly decreased spleen weight (41 and 24%, respectively, less than those of controls); the NOAEL was 150 ppm (Kjellstrand et al. 1983a). Mice exposed to trichloroethylene for 3 hours at ≥10 ppm with simultaneous streptococcal aerosol challenge had increased susceptibility to pulmonary infection with *Streptococcus zooepidemicus* (Aranyi et al. 1986). Increased susceptibility was not observed at 5 ppm following a single 3-hour exposure, or five daily 3-hour exposures. Histopathological effects on the spleen were not observed in squirrel monkeys, rats, guinea pigs, dogs, or rabbits exposed to 700 ppm trichloroethylene 8 hours/day, 5 days/week for 6 weeks, or to 35 ppm continuously for 90 days (Prendergast et al. 1967).

The highest NOAEL values and all LOAEL values from each reliable study for immunological/ lymphoreticular effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.4 Neurological Effects

Studies evaluating neurological effects in humans and animals exposed during gestation are discussed in Section 3.2.1.6 (Developmental Effects).

Experimental exposure studies have attempted to associate various neurological effects in humans with specific trichloroethylene exposure levels. Voluntary exposures of 1–4 hours resulted in complaints of drowsiness at 27 ppm and headache at 81 ppm (Nomiyama and Nomiyama 1977). These are very low

exposure levels, but the results are questionable because of the use of only three test subjects per dose, lack of statistical analysis, sporadic occurrence of the effects, lack of clear dose-response relationships, and discrepancies between the text and summary table in the report. Therefore, this study is not presented in Table 3-1. No effects on visual perception, two-point discrimination, blood pressure, pulse rate, or respiration rate were observed at any vapor concentration in this study. Other neurobehavioral tests were not performed, and the subjects were not evaluated following exposure.

Effects noted from inhalation of trichloroethylene vapors by male volunteers include impaired visual-motor coordination (measured by groove-type hand steadiness, depth perception, and pegboard tests) at 1,000 ppm for 2–2.5 hours (Vernon and Ferguson 1969). Increases in heart and breathing rates were noted when trichloroethylene was inhaled simultaneously with ethanol ingestion at 200 ppm (Windemuller and Ettema 1978). This latter study found no effect without ethanol ingestion. An 8-hour exposure (two 4-hour exposures separated by 1.5 hours) to 110 ppm was reported to result in decreased performance on tests of perception, memory, reaction time, and manual dexterity (Salvini et al. 1971). However, a later attempt to replicate these results found no effects other than fatigue and drowsiness (Stewart et al. 1974a), so the original results remain in doubt.

In contrast to the above reports of acute exposure effects, reports of no effect in humans include no psychomotor impairment at 95 ppm (Konietzko et al. 1975a), no change in visual choice, pursuit rotor, or subjective feelings at 200 ppm (Windemuller and Ettema 1978), and no change in reaction time, hand steadiness, or other behavioral parameters at 300 ppm (Ettema et al. 1975). Each of these studies involved an exposure of <4 hours. No change in reaction time or short-term memory function was seen in 15 subjects exposed to 1,080 mg/m^3 (200 ppm) for 3 days, 70 minutes/day (Gamberale et al. 1976). Somewhat longer exposures of 5 days resulted in psychological changes at 100 ppm as measured by standard psychometric tests (Triebig et al. 1977). Motor and dexterity tests were normal in five to six volunteers exposed to 200 ppm for 5 days, 7 hours/day, although they did complain of fatigue and drowsiness (Stewart et al. 1970). Half of the subjects also indicated that, on one or more occasions after exposure, greater mental effort was required to perform the tests.

In cases of acute accidental or intentional overexposure to trichloroethylene vapors, actual exposure levels are not typically quantified. Trichloroethylene-induced neurological effects include euphoria, giddiness, lethargy, confusion, dizziness, headache, nausea, difficulty swallowing, facial effects that indicate possible trigeminal nerve damage (including sensation deficits, jaw weakness, increased blink reflex latency), which may be irreversible, memory deficits, and unconsciousness (Adamek and Krupiński 2007;

Buxton and Hayward 1967; Carrieri et al. 2007; Clearfield 1970; Feldman 1970; Feldman et al. 1985; James 1963; Lawrence and Partyka 1981; Lachnit and Pietschmann 1960; Leandri et al. 1995; Longley and Jones 1963; Milby 1968; Miller et al. 2002; Pembleton 1974; Thierstein et al. 1960; Troutman 1988). These types of uncontrolled case studies are of limited value in determining the exposure levels associated with the effects of trichloroethylene inhalation under usual occupational and environmental exposures. Also, the lack of information on the subjects' preexisting health and the possibility of effects from other chemicals to which the subjects were exposed further confound the usefulness of this information.

Intermediate- and chronic-duration occupational and nonoccupational exposures to trichloroethylene have produced neurological effects similar to those found in acute exposure situations. Workers chronically exposed to levels between 38 and 172 ppm reported symptoms of sleepiness, dizziness, headache, and nausea, but no apparent trigeminal nerve disorders (El Ghawabi et al. 1973). In a study of Dutch workers regularly exposed to no more than 35 ppm (the Dutch threshold limit value), investigators found no evidence of trichloroethylene-induced trigeminal nerve impairment as measured by blink reflex, but did report an increased latency (38 ms longer than that of controls) for the masseter reflex (another measure of trigeminal nerve function) (Ruijten et al. 1991). A case study of a retired metal degreaser who had been exposed to between 8 and 170 mg/m^3 (1.5 and 32 ppm) for 1–2 hours/day over a period of 20 years reported symptoms of headache, forgetfulness, vertigo, nausea, and loss of feeling in hands and feet persisting for 4 years after retirement (Kohlmuller and Kochen 1994). However, this worker had also been exposed to elevated levels due to accidental spills several times during his career, and it may have been that these few incidences of acute, high-level exposure were more significant factors related to his symptoms, rather than the chronic, low-level exposure. Caprioli et al. (2001) reported loss of strength and polyneuropathy in a woman who had been exposed to trichloroethylene during a 3-month period of degreasing and antiquing processes (7–8 hours/day) in a poorly-ventilated garage.

Murata et al. (2010) reported a significant association ($p<0.001$) between eyes open static postural sway and urinary trichloroethanol in an investigation of 57 workers exposed to trichloroethylene for periods of 0.1–37 years at maximum estimated ambient concentrations <22 ppm; a control group consisted of 60 subjects. Total tremor intensities in nondominant hands differed significantly ($p=0.039$) among three groups of the workers, divided according to cumulative exposure index. Ambient trichloroethylene air concentrations were estimated using the equation $Y=8.37X+17.12$, where X is trichloroethylene in air and Y is total trichloro-compounds (TTC; sum of the trichloroethylene urinary metabolites, trichloroethanol and TCA) (Ogata et al. 1971). Murata et al. (2010) reported a mean TTC level of 4.2 mg/L (range 0.6–

192.6) in the urine from exposed workers; TTC was not detected in the urine of the control subjects. The results of Murata et al. (2010) indicate that even relatively low levels of occupational exposure to trichloroethylene may affect neuromotor function.

Chronic exposure in the workplace has been associated with damage to cranial nerves in several cases (Bardodej and Vyskocil 1956; Barret et al. 1987; Cavanagh and Buxton 1989). Persons who died from overexposure have shown degeneration of cranial nuclei in the brain stem (Buxton and Hayward 1967). Sanz et al. (2008) reported a case of disabling myoclonic encephalopathy with progression to thalamic and cerebellar involvement in a 25-year-old woman with a history of 18 months of occupational exposure to trichloroethylene; neurological symptoms persisted after the woman left the job.

Other reported neurological effects of chronic occupational exposure to unquantified trichloroethylene levels include memory loss (Grandjean et al. 1955; Smith 1966), mood swings (Barret et al. 1987; Milby 1968; Rasmussen et al. 1993d), trigeminal neuropathy (Barret et al. 1987; Feldman et al. 1992; Mitchell and Parsons-Smith 1969; Smith 1966), cranial nerve VIII damage and decreased psychomotor function (Konietzko 1979), impaired acoustic-motor function (Rasmussen et al. 1993c), and psychotic behavior with impaired cognitive function (Steinberg 1981). The study by Feldman et al. (1992) found that the neuropathic effects of trichloroethylene appear to be specific to the trigeminal nerves, rather than generalized. For instance, chronic exposure to trichloroethylene resulted in no change in conduction velocity measured in the radial and ulnar nerves (Triebig et al. 1978). Sympathetic nerve activity, as measured by changes in serum dopamine-β-hydroxylase activity, was normal in workers occupationally exposed to trichloroethylene levels of about 22 ppm (Nagaya et al. 1990). However, some cranial nerves, other than the trigeminal, have shown an exposure-related effect, including the facial (Feldman et al. 1985), olfactory (Rasmussen et al. 1993a), and acoustic nerves. Interestingly, Rasmussen et al. (1993a) reported no significant association ($p=0.42$) between length of exposure and trigeminal nerve effect. There is some evidence that effects on trigeminal nerve function may be due to dichloroacetylene (a trichloroethylene combustion product formed under conditions of high alkalinity or temperature during volatilization of trichloroethylene (Albee et al. 1997, 2006; Barret et al. 1991, 1992; Laureno 1993; Reichert et al. 1976); in one set of animal studies, trigeminal nerve effects were more prominent following exposure to dichloroacetylene than trichloroethylene (Barret et al. 1991, 1992).

Goldman et al. (2012) examined possible associations between exposure to solvents and risk of Parkinson's disease (a neurodegenerative motor disorder). Ninety-nine twin pairs discordant for Parkinson's disease were interviewed regarding lifetime occupations and hobbies; exposures to six

specific solvents were estimated independent of case status. Ever exposure to trichloroethylene was associated with increased risk of Parkinson's disease (OR 6.1; 95% CI 1.2–33; p=0.034).

Trichloroethylene was once used as a surgical anesthetic (Hewer 1943). Some patients were reported to have experienced trigeminal neuropathy following anesthesia using trichloroethylene in association with soda-lime (Humphrey and McClelland 1944). The reaction of trichloroethylene with the soda-lime was thought to have produced dichloroacetylene, which triggered neuropathies in 13 patients over a 4-month period in a county hospital. No new cases were discovered for 3 months after the discontinuation of the use of soda-lime. In another study, Pembleton (1974) found trichloroethylene to be a satisfactory anesthetic using an open technique without soda-lime. A mixture of nitrous oxide and 1,000 ppm of trichloroethylene has been used for obstetrical anesthesia (Crawford and Davies 1975). No adverse effects on infants or their mothers were noted. Trichloroethylene was also used, with variable success, in the treatment of painful symptoms of trigeminal neuralgia (Glaser 1931).

Studies on the neurological effects of acute trichloroethylene inhalation in animals have produced results similar to those observed in human studies. In rats, exposures of ≤8 hours have resulted in decreased electric shock avoidance and frequency of lever press in a Skinner box at 250 ppm (Kishi et al. 1993), decreased swimming time but no change in shuttle box or maze performance at 800 ppm (Grandjean 1963), suppressed reaction to visual stimulus at 14,800 mg/m^3 (2,754 ppm) (Niklasson et al. 1993), lethargy at 3,000 ppm (Adams et al. 1951), and full anesthesia at 4,800 ppm (Adams et al. 1951). Ataxia was observed in rats exposed to 4,380 ppm trichloroethylene 4 hours/day, 5 days/week for 10 days, but not at an exposure level of 1,568 ppm (Goldberg et al. 1964b). Most of these effects were found to be reversible when the exposure period ended. Rats that had been conditioned to climb a rope to a feeding trough in response to a signal exhibited no change in response latency after an 11–14-hour exposure to 200 ppm trichloroethylene, although a significant increase in spontaneous climbs in the absence of a signal was seen (Grandjean 1960). The study authors indicated that this may have been due to increased disinhibition or increased excitability. Exposures of rats for 3 days (4 or 8 hours/day) to 1,000 ppm trichloroethylene resulted in disturbed sleep cycles, while seizures, abnormal electroencephalographic (EEG) activity, and post-exposure cardiac arrhythmia were seen at 3,000 ppm (Arito et al. 1993).

Some animal studies included evaluation of effects of exposure concentration versus time on nervous system function; the results indicate that concentration, rather than time of exposure, is more important in determining effects. In one study, rats were trained to perform a signal detection task that involved the pressing of two levers for food reward: one lever when a light flashed and the second lever produced

food when there was no signal (Bushnell 1997). The trained rats were exposed to 0, 400, 800, 1,200, 1,600, 2,000, or 2,400 ppm trichloroethylene for 0.33, 0.67, or 1 hour. Response times were significantly increased only at 2,400 ppm at 0.67 and 1 hour. Sensitivity was significantly decreased at 2,400 ppm at all exposure times. At 0.33 hour, sensitivity was not affected at the other concentrations. At 0.67 hour, sensitivity was significantly decreased at 2,000, and 1,200 ppm, and at 1 hour, sensitivity was significantly decreased at 2,000, 1,600, and 1,200 ppm. Sensitivity was not affected at any point of time at 800 ppm, and this concentration is considered the NOAEL for this study. In a companion study, it was noted that rats developed tolerance to trichloroethylene during 2 weeks of intermittent exposure as reflected by improvement in performance of the signal detection task following repeated exposures (Bushnell and Oshiro 2000). Boyes et al. (2003, 2005) reported trichloroethylene-induced decreased amplitude of visual evoked potentials in rats repeatedly exposed to trichloroethylene vapors at concentrations in the range of 1,000–5,000 ppm; the results of these studies indicated that momentary brain trichloroethylene level (not exposure duration) is an appropriate dose metric to predict these effects. Results of other studies designed to assess trichloroethylene-induced visual effects include changes in visual evoked potentials (Blain et al. 1992) and electroretinal responses to flash stimulation (Blain et al. 1994) in rabbits exposed to 350 ppm trichloroethylene for 12 weeks (4 days/week, 4 hours/day).

Hearing loss in the mid-frequency range (8–20 kHz) is another effect observed in rats exposed to trichloroethylene. Crofton and Zhao (1993) found significant hearing loss, which persisted for up to 14 weeks post-exposure, exclusively in the 8–16-kHz range when Long-Evans rats were exposed to 4,000 ppm 6 hours/day for 5 days. Rats exposed to 3,500 ppm for 5 days and tested at a wide range of frequencies (0.5–40 kHz) exhibited hearing loss only up to a frequency of 16 kHz, confirming that the effect is specific to the mid-frequency range (Crofton et al. 1994). Assessment of relationships between exposure concentration and duration in the observed trichloroethylene-induced hearing loss in rats included exposures to trichloroethylene vapors using 6-hour exposure times and either single exposure, repeated exposures for 5 days, or exposures 5 days/week for 4 or 13 weeks (Boyes et al. 2000; Crofton and Zhao 1997). Following the final exposure period, the auditory threshold to a 16 kHz tone was measured and compared to that of a group of air-exposed rats. A single 6-hour exposure at 6,000 ppm resulted in a 14 dB increase in the 16 kHz threshold (NOAEL 4,000 ppm). Significantly increased 16 kHz threshold was noted at 3,200 ppm in the groups exposed for 5 days or 4 weeks, and 13 weeks of exposures at 2,400 ppm resulted in a 21 dB increase in the 16 kHz threshold (NOAEL 1,600 ppm). No hearing loss was detected after a 5-day exposure to 1,500 ppm, as measured by brainstem auditory evoked response, but a substantial effect was seen when this level was combined with 500 ppm styrene (Rebert et al. 1993). Hearing loss at 20 kHz only was measured in Wistar rats exposed 18 hours/day, 5 days/week

for 3 weeks to 3,000 ppm and a reduced acoustic startle response was observed in rats at 1,500 ppm (Jaspers et al. 1993). A depressed auditory sensory evoked potential amplitude was seen in F344 rats exposed to 2,000 ppm for 3 weeks and 3,200 ppm for 12 weeks (Rebert et al. 1991). This latter study found no effect at 1,600 ppm in Long-Evans rats and thus set the response threshold at about 2,000 ppm trichloroethylene. F344 rats exposed to 2,500 ppm trichloroethylene for 13 weeks (5 days/week, 6 hours/day) exhibited a decrease in tone pip auditory response primarily at 16 kHz, along with a loss of cochlear hair cells (NOAEL 800 ppm) (Albee et al. 1993, 2006). Similar ototoxic effects were reported by Muijser et al. (2000) following exposure of rats to trichloroethylene at 3,000 ppm for 18 hours/day, 5 days/week for 3 weeks. Fechter et al. (1998) reported that the ototoxicity of trichloroethylene in rats could be accounted for by loss of spiral ganglion cells in the middle turn of the cochlea.

Other studies assessed clinical signs of trichloroethylene-induced behavioral effects. After 10 days of exposure, reduced social behavior and reduced exploratory behavior were observed in rats exposed to 100 ppm trichloroethylene 6 hours/day 5 days/week for a total of 5 weeks (Silverman and Williams 1975). Waseem et al. (2001) exposed rats to trichloroethylene vapors at 376 ppm, 4 hours/day, 5 days/week for 180 days and noted significantly increased spontaneous locomotor activity. In rats exposed to 50 or 100 ppm trichloroethylene 8 hours/day, 5 days/week for 6 weeks, effects on sleep patterns were observed (Arito et al. 1994a). At 50 ppm, decreased wakefulness was observed during the exposure. Effects remaining at 22 hours after the end of the 6-week exposure included decreased heart rate during sleep at 50 ppm and decreased wakefulness at 100 ppm (Arito et al. 1994a). An 18-week exposure (16 hours/day, 5 days/week) to 1,000 ppm resulted in increased latency in visual discrimination tasks, but not in spontaneous activity, coordinated movement, grip strength, or peripheral nerve conduction time (Kulig 1987). Impaired swimming behavior was observed in rats exposed to 400 ppm trichloroethylene 8 hours/day, 5 days/week for 44 weeks (Battig and Grandjean 1963). An increased level of exploratory activity immediately after exposure, attributed to reduced anxiety on the part of the rats, was also observed in this study. Decreased avoidance was observed in rats exposed to 125 ppm trichloroethylene 4 hours/day, 5 days/week for 30 days (Goldberg et al. 1964a).

One study evaluated the effect of trichloroethylene on heart rate. Among rats of various ages, the normal age-related decrease in heart rate and circadian rhythm amplitude, as well as the incidence of spontaneous bradyarrhythmias, were exacerbated by an 8-hour exposure to 300 ppm of trichloroethylene, followed by exposure to 1,000 ppm for 8 hours 7 days later (Arito et al. 1994b).

Biochemical changes have also been noted in the brains of animals after an inhalation exposure to trichloroethylene. Decreased brain ribonucleic acid (RNA) content was seen in rats exposed to 200 ppm for 6 hours/day for 4 days (Savolainen et al. 1977). Open-field activity, preening, and rearing were increased in these rats at 1 hour, but not 17 hours, post-exposure. In gerbils, continuous exposure to 60 ppm trichloroethylene for 3 months, followed by a recovery period of 4 months, resulted in increased brain S100 protein content, consistent with astroglial hypertrophy and proliferation (Haglid et al. 1981). Exposure to 320 ppm produced significantly elevated DNA content in the cerebellar vermis and sensory motor cortex. It is not known whether such effects reflect adverse changes.

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

3.2.1.5 Reproductive Effects

Possible associations between exposure to organic solvents (including trichloroethylene) and measures of fertility and fecundity have been assessed to some extent in occupationally-exposed men and women. Increases in miscarriages have been reported among nurses exposed to unspecified concentrations of trichloroethylene and other chemicals in operating rooms (Corbett et al. 1974). The occurrence of miscarriages could not conclusively be attributed to trichloroethylene because there was concomitant exposure to other chemicals. A retrospective case-control study conducted in humans compared spontaneous abortion rates among women who had been exposed occupationally or nonoccupationally to trichloroethylene and other solvents to rates among women without solvent exposure (Windham et al. 1991). The authors observed approximately three times the risk of spontaneous abortion with exposure to trichloroethylene. This risk increased further when women with less than a half hour of exposure to trichloroethylene each week were excluded from the analysis. However, a consistent dose-response relationship was not observed, and most of the women were exposed to a variety of solvents, not just trichloroethylene. Other epidemiologic studies have evaluated possible associations between occupational exposure of women to organic solvents (including trichloroethylene) and measures of fertility including time-to-pregnancy, spontaneous abortion, and menstrual cycle disturbance (Bardodej and Vyskocil 1956; Corbett et al. 1974; Lindbohm et al. 1990; Sallmén et al. 1995; Taskinen et al. 1994; Windham et al. 1991; Zielinski 1973). Some of these studies provide suggestive evidence of an association between exposure to trichloroethylene and reduced fecundability (Sallmén et al. 1995) and menstrual cycle disturbances (including amenorrhea) (Bardodej and Vyskocil 1956; Sagawa et al. 1973; Zielinski 1973).

Studies in men include assessments of reproductive behavior, sperm quality, and fertility. Bardodej and Vyskocil (1956) reported decreased potency or unspecified sexual disturbances in a group of 75 men employed in dry cleaning or metal degreasing processes. El Ghawabi et al. (1973) reported decreased libido in a group of 30 men employed in a money printing shop for up to 5 years and exposed to trichloroethylene at 38–172 ppm; however, the study authors indicated that the decreased libido was likely due to fatigue and sleepiness. Within two groups of men (n=85) exposed to trichloroethylene during degreasing of electronics at a mean trichloroethylene air concentration of 29.6 ppm (range 9–131 ppm, determined by 8-hour personal air sampling for 12 of the men), a decreased percentage of normal sperm morphology was reported for 48 of the workers with higher levels of trichloroethylene exposure (as determined by urinary TCA ≥25 mg/g creatinine) compared to 37 of the workers with lower levels of trichloroethylene exposure (Chia et al. 1996; 1997; Goh et al. 1998). There was no effect on sperm volume, density, or motility; however, prevalence of hyperzoospermia increased with increasing urinary TCA level. Sallmén et al. (1998) found no effect on male fertility in a study that examined paternal occupational exposure to trichloroethylene and time-to-pregnancy among their wives. Levels of exposure were determined by questionnaire and urinary TCA levels; however, the presentation of data regarding exposure categories and fertility outcomes precludes meaningful dose-response assessment. Forkert et al. (2003) identified trichloroethylene and its metabolites in the seminal fluid of eight mechanics exposed to trichloroethylene for at least 2 years and diagnosed with clinical infertility. Neither trichloroethylene nor its metabolites were detected in the seminal fluid of five other clinically infertile men at the same clinic who had not been occupationally exposed to trichloroethylene; furthermore, the study did not include controls exhibiting normal fertility. As noted in Section 3.2.2.2 (Endocrine Effects), there is some evidence of an association between occupational exposure to trichloroethylene and decreases in serum levels of testosterone, follicle-stimulating hormone, and sex-hormone binding globulin (Chia et al. 1997; Goh et al. 1998).

Studies in animals demonstrate the toxicity of trichloroethylene to the male reproductive system. Repeated exposures of male rats at trichloroethylene concentrations of 376–1,000 ppm for as little as 1–2 weeks resulted in effects that included degeneration of epididymal epithelium (Kan et al. 2007), increases in abnormal sperm and decreased reproductive success (Kumar et al. 2000b), and decreased numbers of sperm capable of attaching to eggs *in vitro* (Xu et al. 2004). Kumar et al. (2000a, 2000b, 2001b) exposed male rats to trichloroethylene at 376 ppm for 4 hours/day, 5 days/week for up to 24 weeks and noted testicular atrophy and decreases in sperm count and motility. Forkert et al. (2002) reported epididymal epithelium damage in mice exposed to trichloroethylene vapors at 1,000 ppm,

6 hours/day, 5 days/week for 4 weeks. Other mice exposed to 2,000 ppm of trichloroethylene, 4 hours/day for a 5-day period, exhibited a significant increase in abnormal sperm morphology of 1% 28 days after the exposure (NOAEL 200 ppm) (Land et al. 1981). A 6% increase in abnormal sperm was observed 4 weeks, but not 4 days or 10 weeks, after mice were exposed to 100 ppm trichloroethylene 7 hours/day for 5 days (Beliles et al. 1980). Based on the time after exposure at which sperm were affected, the study authors indicated that trichloroethylene damages sperm precursor cells but that spermatogonia were either unaffected or were capable of recovery. Reproductive performance was not tested in most of the animal studies. Another mouse study tested the effects of a 5-day exposure (6 hours/day) on spermatid micronuclei frequency; no effects were observed at exposure levels of up to 500 ppm, the highest concentration tested (Allen et al. 1994). These results were interpreted as evidence that trichloroethylene did not cause meiotic chromosome breakage or loss. No treatment-related reproductive effects were seen in female rats exposed to 1,800 ppm trichloroethylene for 2 weeks (6 hours/day, 7 days/week) before mating (Dorfmueller et al. 1979).

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

3.2.1.6 Developmental Effects

No increase in malformed babies was observed among approximately 2,000 fathers and mothers exposed to unspecified concentrations of trichloroethylene in the workplace (Tola et al. 1980).

A retrospective case-control study conducted in humans compared spontaneous abortion rates among women who had been exposed occupationally or nonoccupationally to trichloroethylene and other solvents to rates among women without solvent exposure (Windham et al. 1991). The authors observed about a 3-fold increase in risk of spontaneous abortion associated with exposure to trichloroethylene. This risk increased further when women with less than a half hour of exposure to trichloroethylene per week were excluded from the analysis. However, a consistent dose-response relationship was not observed, and most of the women were exposed to a variety of solvents other than trichloroethylene. In this same study, the relationship between exposure to halogenated solvents during the first 20 weeks of pregnancy and fetal growth were examined. No association between exposure to solvents and decreased fetal growth was observed. However, the number of small infants was too low to specifically assess trichloroethylene exposures, and most fetal growth would occur after the first 20 weeks of pregnancy.

No associations were observed between occupational exposure to trichloroethylene and rates of spontaneous abortion among women who reported occupational exposure to organic solvents including trichloroethylene (OR 0.6 [95% CI 0.2–2.3]; based on 4 exposed cases and 3 controls and adjusted for exposure to other solvents) (Lindbohm et al. 1990), or women whose husbands were exposed to trichloroethylene (OR 1.0 [95% CI 0.6–2.0]; based on 17 exposed cases and 35 referents and adjusted for exposure to other solvents) (Taskinen et al. 1989). However, these studies are limited by small incidences of spontaneous abortion.

Yauck et al. (2004) reported results of a case-control study of 4,025 infants born to mothers in Milwaukee, Wisconsin, between 1997 and 1999. The study included a trichloroethylene-exposed group (defined as residing within a 1.32-mile radius of a trichloroethylene-emitting site) and a nonexposed group (residing outside a 1.32-mile radius of a trichloroethylene-emitting site). Using nonexposed mothers <38 years of age as the referent, there was no significant increased risk of congenital heart defects in children from trichloroethylene-exposed mothers <38 years of age (OR 0.9; 95% CI 0.6–1.2). However, a 6.2-fold increased risk of congenital heart defects was noted for children of trichloroethylene-exposed mothers who were ≥38 years of age at delivery (OR 6.2; 95% CI 2.6–14.5), and a 1.9-fold increased risk of congenital heart defects was also noted for children of unexposed mothers who were ≥38 years of age at delivery (OR 1.9; 95% CI 1.1–3.5). These results indicate that maternal age at delivery may influence the risk of congenital heart defects in children of trichloroethylene-exposed mothers.

Analyses of birth outcome were performed in the Endicott, New York area where residents may have been exposed to volatile organic compounds (VOCs) via soil vapor intrusion (migration of contamination through the soil into structures through cracks in building foundations) (ATSDR 2006, 2008; Forand et al. 2012). Groundwater sampling performed following a 1979 spill of 4,100 gallons of 1,1,1-trichloroethane at a manufacturing facility revealed a large plume of contaminants including trichloroethylene (NYSDEC 2003). Initially, it was assumed that the VOC-contaminated groundwater was not of particular health concern because residential drinking water was supplied primarily from wells outside the plume area. Subsequently, it was determined that exposure could occur via soil vapor intrusion; soil vapor sampling initiated in 2000 revealed that trichloroethylene was the predominant contaminant in the soil vapor above the plume region where levels typically ranged from 100 to 10,000 μg/m^3 (18–1,800 ppb) (McDonald and Wertz 2007; NYSDEC 2003). Trichloroethylene levels in indoor air samples in the plume area ranged from 0.18 to 140 μg/m^3 (0.0324–25.2 ppb) (Agency for Toxic Substance and Disease Registry 2006; NYSDEC 2003). Sixty-seven percent of the measured indoor trichloroethylene samples were higher than

the upper 95th percentile trichloroethylene level of 3.3 μg/m^3 (0.59 ppb) determined from data compiled from 15 U.S. indoor air studies that measured background concentrations of VOCs in homes not expected to be influenced by soil vapor intrusion (EPA 2011g). The evaluations of ATSDR (2006, 2008) and Forand et al. (2012) included assessment of birth outcomes among those residents in the plume area compared to birth outcomes in the rest of New York State exclusive of New York City.

In the evaluation by ATSDR (2006, 2008), total cardiac defects were twice as prevalent as expected (standardized prevalence ratio [SPR] 2.02; 95% CI 1.23–3.11). There were no cases of neural tube defects, orofacial clefts, or choanal atresia in the study area, and results of spontaneous fetal death analysis did not support an association between living in the exposure area and increased risk of fetal death.

In the evaluation of Forand et al. (2012), adjusted rate ratios were elevated for low birth weight (rate ratio 1.36; 95% CI 1.07–1.73; n=76), small for gestational age (rate ratio 1.23; 95% CI 1.03–1.48; n=117), term low birth weight (rate ratio 1.68; 95% CI 1.20–2.34; n=37), cardiac defects (rate ratio 2.15; 95% CI 1.27–3.62; n=15), and conotruncal defects (rate ratio 4.91; 95% CI 1.58–15.24; n=3). It was noted that residual socioeconomic confounding may have contributed to low birth weight outcomes.

A case-control study evaluated the risk of autism spectrum disorder in a population of children exposed during gestation and early life in southwestern Pennsylvania (Talbott et al. 2015). Trichloroethylene was one of numerous solvents and chemicals measured in air. Trichloroethylene concentrations were stratified by quartile and ranged from approximately 71 mg/m^3 for the second quartile to approximately 83 mg/m^3 for the fourth quartile. Cases (n=217), born 2005–2009, were compared to matched controls (n=224). The ORs for quartiles 2 through 4 were similar; the OR (95% CI) for the fourth quartile was 1.22 (0.68–2.17).

Pregnant laboratory animals have been exposed to trichloroethylene vapors, but no conclusive studies have been encountered that clearly indicate teratogenic effects. There were no indications of trichloroethylene exposure-related developmental effects in pups of rat or mouse dams exposed to 100–600 ppm of trichloroethylene during gestation (Beliles et al. 1980; Carney et al. 2006; Hardin et al. 1981; Healy et al. 1982; Schwetz et al. 1975). Decreased fetal weight and incomplete skeletal ossification were observed in offspring of rats exposed to 1,800 ppm trichloroethylene 6 hours/day on GDs 0–20 (Dorfmueller et al. 1979). Activity measurements completed in the offspring at ages 10, 20, and 100 days did not show an effect of trichloroethylene exposure. Developmental effects were not observed in

offspring of mice exposed to 300 ppm trichloroethylene 7 hours/day on GDs 6–15 (Schwetz et al. 1975). Although not statistically significant, four rabbit fetuses in 2 of 23 litters had external hydrocephalus (Beliles et al. 1980; Hardin et al. 1981). Because this effect is rarely observed in control rabbits, the study authors indicated that it was suggestive of a teratogenic effect, although it was not conclusive. Therefore, this study is not presented in Table 3-1 or Figure 3-1.

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

3.2.1.7 Cancer

Cancer Classifications. The potential carcinogenicity of inhaled trichloroethylene has been evaluated in numerous epidemiological studies and experimental animal studies. HHS has classified trichloroethylene as "*known to be a human carcinogen*" based on sufficient evidence of carcinogenicity from humans (NTP 2016). IARC (2014) has classified trichloroethylene as "carcinogenic to humans" based on sufficient evidence in humans (Group 1). EPA (2011e) has characterized trichloroethylene as "carcinogenic in humans by all routes of exposure."

Epidemiological Studies. A large number of cohort and case-control studies have assessed possible associations between inhalation exposure to trichloroethylene and cancer, with comprehensive reviews conducted by NTP (2016), EPA (2011e), and IARC (2014). NTP (2016) concluded that trichloroethylene causes kidney cancer in humans based on consistent results of epidemiological studies and has a causal association with non-Hodgkin's lymphoma based on results of several epidemiological studies; however, the epidemiological evidence for non-Hodgkin's lymphoma is less consistent than for kidney cancer. For other cancer types, NTP (2016) concluded that evidence from epidemiological studies is inadequate to evaluate associations. Conclusions of the EPA (2011e) Toxicological Review regarding epidemiological evidence for cancer are similar to the conclusions of NTP (2016): convincing evidence for a causal relationship for trichloroethylene and kidney cancer; strong evidence for a causal relationship for non-Hodgkin's lymphoma, but less consistent that that for kidney cancer; limited evidence for liver cancer; and less evidence for other cancer types. IARC (2014) concluded that the epidemiological evidence for kidney cancer is sufficient to establish a causal relationship, and "positive associations" have been observed for non-Hodgkin's lymphoma and liver cancer. The National Research Council of the National Academy of Sciences (NRC 2006, 2009) concluded that there is inadequate/insufficient evidence to determine associations between trichloroethylene and hepatobiliary cancer and non-Hodgkin's

lymphoma. Furthermore, NRC (2006) concluded that exposure to trichloroethylene at levels relevant to the general public is not likely to induce liver cancer in humans. Recently published reviews on the carcinogenicity of trichloroethylene in humans and laboratory animals, and the role of trichlorethylene biotransformation in mutagenicity and carcinogenicity, may be consulted for additional information (Cichocki et al. 2016; Lash et al. 2014; Rusyn et al. 2014).

Table 3-2 provides an overview of selected epidemiological studies, including information on study types (e.g., cohort, case-control), study populations, exposure assessments (qualitative versus semi-quantitative, assessment methods), consideration of confounders, and study strengths and limitations. Studies were selected based on the following considerations:

- studies that EPA (2011e) selected for inclusion in meta-analyses on kidney cancer, non-Hodgkin's lymphoma, and liver cancer;
- studies on other cancer end points (cancers other than kidney, liver, and non-Hodgkin's lymphoma) meeting the following criteria as listed in EPA (2011e): cohort or case-control study design; evaluation of incidence or mortality; adequate selection in cohort studies of exposure and control groups and of cases and controls in case-control studies; trichloroethylene exposure potential inferred to each subject and quantitative assessment of trichloroethylene exposure assessment for each subject by reference to industrial hygiene records indicating a high probability of trichloroethylene use, individual biomarkers, job-exposure matrices, or obtained from subjects using questionnaire (case-control studies); and
- studies meeting the EPA (2011e) criteria that were published after 2011.

For additional details and reviews of these and other epidemiological studies assessing the potential carcinogenicity of trichloroethylene, the EPA Integrated Risk Information System (IRIS) Toxicological Review for Trichloroethylene (EPA 2011e), IARC (2014), and NTP (2016) may be consulted. Additional information is also provided in an assessment on studies of drinking water contaminants, including trichloroethylene, at U.S Marine Corp Base at Camp Lejeune conducted by ATSDR (2017b).

As summarized in Table 3-2, selected studies included 9 meta-analyses, 1 pooled case-control study, 12 cohort studies, and 32 case-control studies. Study populations were from numerous countries, including the United States, Canada, and several European countries. Cohort studies evaluated general worker populations, microelectronics/machine workers, and aircraft and aerospace workers. The Radican et al. (2008) cohort study is a follow-up of Blair et al. (1998). Most case-control studies evaluated various cancer end points in adult worker populations from numerous industries. Three case-control studies examined cancer in children of exposed workers (DeRoos et al. 2001; McKinney et al. 1991; Shu et al. 1999).

Table 3-2. Overview of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Cancer

Reference; population	Exposure assessment	Confounders considered	Strengths and limitations[a]
Meta-analyses			
Alexander et al. 2006; Workers from 8 studies	JEM and/or urine trichloroethylene	Not reported for individual studies	Strengths[b]: large number of participants; results consistent across studies Limitations[b]: participants likely exposed to other chemicals and solvents; no information on potential impact of confounding factors
Alexander et al. 2007; Workers from 15 studies	JEM and/or urine trichloroethylene	Not reported for individual studies	Strengths[b]: large number of participants Limitations[b]: participants likely exposed to other chemicals and solvents; no information on adjustments for potential confounding factors
EPA 2011a; Scott and Jinot 2011 Workers from 24 studies	JEM and/or urine trichloroethylene	"Most studies" considered age and sex	Strengths: includes numerous well-controlled studies; large number of participants; evaluated publication bias Limitations: low-to-moderate heterogeneity for NHL data
Hansen et al. 2013; Workers from 3 Nordic studies	urine trichloroethylene	Age; sex; country; calendar year	Strengths[b]: large number of participants; prospective design; long follow-up period; used national registry for cancer Limitations[b]: lack of information on potential confounders (smoking, alcohol use); no information on duration of exposure
Karami et al. 2013 Workers from 28 studies	JEM and/or urine trichloroethylene	Not reported for individual studies	Strengths[b]: participants had known trichloroethylene exposure; low misclassification bias; exposure classification accounted for exposure to other solvents Limitations[b]: most studies lacked subject-specific exposure measurements; use of biomarker measurements may not reflect long-term exposure levels; study selection bias
Kelsh et al. 2010; Workers from 20 studies	JEM and/or urine trichloroethylene	Not reported for individual studies	Strengths[b]: examined heterogeneity across studies; conducted sensitivity and influence analysis Limitations[b]: no information on potential impact of confounding factors; lack of quantitative exposure assessment

Table 3-2. Overview of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Cancer

Reference; population	Exposure assessment	Confounders considered	Strengths and limitations[a]
Mandel et al. 2006; Workers from 7 studies	JEM	Not reported for individual studies	Strengths[b]: known trichloroethylene exposure; assessed heterogeneity Limitations[b]: variability across studies; limited exposure assessments; inconsistent results across studies; no adjustments for potential confounding factors
Ojajärvi et al. 2001; Workers from 5 studies	JEM and/or urine trichloroethylene	Not reported for individual studies	Strengths[b]: participants had known trichloroethylene exposure; publication bias unlikely Limitations[b]: no adjustments for potential confounding factors; exposure to other chemicals
Wartenberg et al. 2000; Workers from 4 studies	JEM and/or urine trichloroethylene	"Few traditional confounding variables (e.g., smoking, alcohol consumption)" were assessed in individual studies	Strengths[b]: High confidence in trichloroethylene exposure; long follow-up periods (17–36 years) Limitations[b]: exposure to other solvents; no assessment of other potential risk factors; short-term urine measurements of trichloroethylene does not reflect long-term exposure; "traditional" confounding factors not considered
Cohort studies			
Anttila et al. 1995; Workers (Finland)	Urine levels of trichloroethylene; no quantitative exposure	Age; sex; calendar year	Strengths: long follow-up period (26 years); data obtained from Finnish registries Limitations: limited statistical power; length of exposure uncertain; selection of participants not described; potential exposure to multiple solvents
Axelson et al. 1994; Male workers (Sweden)	Urine levels of trichloroethylene; no quantitative exposure	Age; calendar year	Strengths: biological monitoring conducted Limitations: exposure was considered "low" in most participants; uncertainty regarding duration of exposure; selection of participants not described
Blair et al. 1998; Aircraft workers (United States)	JEM; no quantitative exposure	Age; sex; race; date of hire; calendar year of death	Strengths[b]: large worker cohort; use of internal comparisons to minimize selection and socioeconomic bias; extended follow-up period Limitations[b]: exposures to multiple chemicals; no information on other risk factors (smoking, alcohol use, diet)

Table 3-2. Overview of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Cancer

Reference; population	Exposure assessment	Confounders considered	Strengths and limitations[a]
Boice et al. 1999; Aircraft workers (United States)	JEM; no quantitative exposure	Birth date; race; sex; duration of exposure; date first employed; employment end date	Strengths: large population; long follow-up period (20–37 years) Limitations: no adjustment for smoking; no monitoring data; exposure to other solvents
Boice et al. 2006; Aircraft workers (United States)	JEM; no quantitative exposure	Birth year; year of hire; potential hydrazine exposure	Strengths: long follow-up period (up to 50 years); accounted for exposure to hydrazine Limitations: referent population not identified; no air or biological monitoring; possible exposure misclassification; did not adjust for smoking
Buhagen et al. 2016; Workers (Norway)	JEM; no quantitative exposure	None reported	Strengths[b]: long observation period (up to 50 years) Limitations[b]: exposure to other chemicals and solvents; did not adjusted for age, race, smoking, or other potential confounding factors
Hansen et al. 2001; Workers (Denmark)	Trichloroethylene in urine or breath; no quantitative exposure	Age; sex; calendar year	Strengths: biological monitoring to determine exposure; medical records obtained from national surveillance program Limitations: measurements of trichloroethylene below the level of detection for 5% of participants; did not adjust for smoking or exposure to other chemicals
Morgan et al. 1998; Workers (United States)	JEM; semi-quantitative exposure	Age; sex; race; calendar year	Strengths: semi-quantitative exposure Limitations: potential exposure misclassification
Raaschou-Nielsen et al. 2003; Workers (Denmark)	JEM; no quantitative exposure	Age; sex; calendar year	Strengths: medical records obtained from national surveillance program Limitations: only a small fraction of the cohort exposed to trichloroethylene; no monitoring data; did not adjust for smoking or exposure to other chemicals

Table 3-2. Overview of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Cancer

Reference; population	Exposure assessment	Confounders considered	Strengths and limitations[a]
Radican et al. 2008; Aircraft maintenance workers (United States); follow-up to Blair et al. 1998	JEM; no quantitative exposure	Age; sex; race	Strengths[b]: large study population; long follow-up period (1952–2000) Limitations[b]: small number of trichloroethylene-exposed deaths and reduced statistical power; did not control for smoking or exposure to other chemicals and solvents; exposure based on job descriptions and other historical information may result in misclassification of exposure
Silver et al. 2014; Microelectronics and Machine workers (United States)	JEM; no quantitative exposure	Age; sex; chemical exposures; birth cohort; changes in exposure levels; time since last exposure; hire era; employment duration prior to 1969	Strengths[b]: long follow-up period (>25 years); Limitations[b]: young age of cohort (only17% deceased); lack of exposure data on workers prior to 1974; incomplete exposure data; lack of data on variability of exposure
Zhao et al. 2005; Aerospace workers (United States)	JEM; no quantitative exposure	Time since first employment; SES; age at event	Strengths[b]: use of cancer registry; evaluated incidence and mortality Limitations[b]: potential exposure misclassification; no information on jobs held before or after employment at facility; no adjustment for smoking; exposure to other chemicals and solvents
Pooled case-control studies			
Cocco et al. 2013; Workers (4 European studies)	JEM; semi-quantitative exposure	Age; sex; study area	Strengths[b]: large study size; high-quality exposure assessment; no heterogeneity across studies; histological confirmed diagnosis Limitations[b]: small number of exposed cases; individual studies used different designs and controls; did not assess exposure to other chlorinated solvents; did not adjust for other confounders (smoking, education, BMI, family history of hematopoietic cancers)

Table 3-2. Overview of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Cancer

Reference; population	Exposure assessment	Confounders considered	Strengths and limitations[a]
Case-control studies			
Brüning et al. 2003; Workers (Germany)	JEM; no quantitative exposure	Age; gender; smoking	Strengths[b]: exposure assessment classified for each participant using JEM Limitations[b]: small number of participants; could not assess confounding from other chemicals or solvents; did not control for hypertension; potential for exposure misclassification
Charbotel et al. 2006; Workers (France)	JTEM; semi-quantitative exposure	Age; sex; BMI; smoking	Strengths: high exposure prevalence; detailed exposure assessment Limitations: low participation rate
Charbotel et al. 2013; Female workers (France)	TEM; no quantitative exposure	SES; SOC; gynecological history; BMI	Strengths[b]: reduced selection and measurement biases by recruiting controls from the same physicians and geographic location as cases Limitations [b]: low mean age of subjects (36 years); cases and controls differed on HPV infection (cases: 100%; controls: 5.8%)
Christensen et al. 2013; Workers (Canada)	Subject reported job history and expert assessment; semi-quantitative exposure	Age; income; educational; ethnicity (French-Canadian versus others); questionnaire respondent (self versus proxy); smoking; coffee intake; aromatic amines exposure	Strengths[b]: reliable semiquantitative exposure information, based on expert assessment after detailed interviews regarding occupational history; controlled for potentially important confounders Limitations[b]: no quantitative exposure measurements of personal exposure to each solvent; estimated temporal trends and industry and occupation-specific profiles; potential confounding by unmeasured risk factors or residual confounding by measured risk factors
Cocco et al. 2010; Workers (multiple countries)	JEM; no quantitative exposure	Age; gender; education; study center	Strengths: detailed exposure assessment Limitations: low response rate from two study centers
Costantini et al. 2008; Workers (Italy)	JEM; no quantitative exposure	Age; gender; education; study area	Strengths[b]: detailed exposure assessment Limitations[b]: none reported

Table 3-2. Overview of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Cancer

Reference; population	Exposure assessment	Confounders considered	Strengths and limitations[a]
DeRoos et al. 2001; Children (United States and Canada)	Self-reported exposure and JEM; no quantitative exposure	Child's age; maternal race; maternal age; maternal education	Strengths[b]: evaluation of exposure misclassification Limitations[b]: potential for "false negative" exposure classification
Dosemeci et al. 1999; Workers (United States)	JEM; no quantitative exposure	Age; smoking; hypertension; diuretic use; use of anti-hypertension medication; BMI	Strengths: large sample size; detailed work and task histories Limitations: lack of direct exposure information; potential exposure misclassification due to next-of-kin interviews
Dumas et al. 2000; Workers (Canada)	JEM; no quantitative exposure	Age; education; respondent status; smoking; beer consumption; BMI	Strengths[b]: histologically confirmed cancer incidence Limitations[b]: potential exposure misclassification; limited statistical power due to low exposure prevalence; small number of participants; included several non-occupational variables as co-variates
Fredriksson et al. 1989; Workers (Sweden)	JEM; no quantitative exposure	Age; sex; scoring index of physical activity	Strengths: use of cancer registry to define diagnosis of rectal cancer; obtained specific information regarding job duties for all jobs Limitations: exposure potential obtained from mailed questionnaires; potential for exposure misclassification; low exposure prevalence to trichloroethylene
Gold et al. 2011; Workers (United States)	JEM; hours of weekly exposure; estimated cumulative exposure	Sex; age; race; education; cancer registry	Strengths[b]: use of detailed occupational information to improve assessment of solvent exposure Limitations[b]: low participation rates; inability to examine race, SES, and solvent exposure; potential for selection bias; small numbers of subjects with exposure to individual chlorinated solvents with limited statistical power
Greenland et al. 1994; Workers (United States)	JEM; no quantitative exposure	Age; year of death	Strengths: none reported Limitations: high likelihood of misclassification bias; deaths likely to be underestimated; missing information from approximately 35% of participants for participants with death in the earlier years; low statistical power

Table 3-2. Overview of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Cancer

Reference; population	Exposure assessment	Confounders considered	Strengths and limitations[a]
Hadkhale et al. 2017; Workers (Finland, Iceland, Norway, Sweden)	JEM; estimated quantitative exposure	Age; sex; quantified exposures to ionizing radiation, asbestos, benzo[a]pyrene, diesel engine exhaust, and sulfur dioxide	Strengths[b]: large study population; controlled for exposure to multiple other agents and variation in exposure levels over time Limitations[b]: no information about smoking
Heineman et al. 1994; Workers (United States)	JEM; no quantitative exposure	Age; year of death; study area	Strengths: large sample size; detailed work histories, including tasks; comprehensive exposure analysis Limitations: lack of direct exposure information; potential exposure inaccuracies for information obtained from next of kin
Kernan et al. 1999; Workers (United States)	JEM; no quantitative exposure	Age; metropolitan status; region of residence; marital status	Strengths: large sample size (total cases: 63,097; total controls: 252,386) Limitations: likely exposure misclassification; total cases per race and sex not reported
Krishnadasan et al. 2007; Workers (Denmark)	JEM; semi-quantitative exposure	Age at diagnosis; occupational activity; pay status; other chemicals (benzene, polycyclic aromatic hydrocarbons, mineral oil, hydrazine)	Strengths: long follow-up period for morality; provided semi-quantitative exposure assessment (low, moderate, high); adjustment for exposure to other chemicals Limitations: potential for exposure misclassification; did not control for race; smoking history not available for all participants
Mattei et al. 2014; Workers (France)	JEM; no quantitative exposure	Age at interview; department; smoking history; number of jobs held; occupational exposure to asbestos; SES	Strengths[b]: large number of subjects Limitations[b]: almost all participants exposed to other solvents; small number of exposed women compared to exposed men, leading to wide confidence intervals
McKinney et al. 1991; Children of workers (United Kingdom)	JEM; no quantitative exposure	Age; sex; region of residency at diagnosis	Strengths: none reported Limitations: low prevalence of trichloroethylene exposure; discordant pairs limited statistical power
Miligi et al. 2006; Workers (Italy)	JEM; no quantitative exposure	Age; sex; education; area	Strengths: none reported Limitations: low statistical power due to low prevalence of exposure; bias likely due to unblinded interviewers

Table 3-2. Overview of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Cancer

Reference; population	Exposure assessment	Confounders considered	Strengths and limitations[a]
Moore et al. 2010; Workers (4 European countries)	JEM; no quantitative exposure	Age; sex; center	Strengths: high confidence in exposure Limitations: low prevalence of exposure
Neta et al. 2012; Workers (United States)	JEM/JTEM; no quantitative exposure	Age at diagnosis; sex; race/ethnicity; hospital site and residential zone; smoking; education; estimated cumulative occupational exposures to lead, magnetic fields, herbicides, and insecticides	Strengths[b]: hospital-based design allowed for rapid ascertainment of newly diagnosed cases; interview of cases and controls under similar conditions; robust exposure assessment, including exposure intensity; assessed cumulative exposure to other agents Limitations[b]: limited power to evaluate exposure-response relationships given the small numbers of subjects; potential exposure misclassification; impaired recall ability of glioma patients regarding past exposures
Nordstrom et al. 1998; Workers (Sweden)	JEM; no quantitative exposure	Age; sex; county of residence	Strengths: histologically confirmed cases; use of national cancer registry Limitations: limited statistical power due to low exposure prevalence and small number of participants
Persson and Fredriksson 1999; Workers (Sweden)	JEM; no quantitative exposure	Age; sex	Strengths: histologically confirmed cases; use of national cancer registry Limitations: small number of participants; potential for exposure misclassification
Pesch et al. 2000; Workers (Germany)	JEM/JTEM; hospital records; no quantitative exposure	Age; smoking; study center	Strengths: population-based selection of controls; use of a JEM and a JTEM to assess exposure Limitations: Most cases did not have substantial exposure
Pesch et al. 2000; Germany (Germany)	JEM/JTEM; hospital records; no quantitative exposure	Age; smoking; study center	Strengths: population-based selection of controls; use of a JEM and a JTEM to assess exposure Limitations: grouping of bladder, ureter, and renal pelvis neoplasms; lower response rate of controls compared to cases; reliance of self-reported information for exposure assessment
Purdue et al. 2011; Workers (United States)	JEM; semi-quantitative exposure	Age; sex; race; education; group and center	Strengths: detailed exposure assessment; histologically confirmed cases; estimated semi-quantitative exposure Limitations: potential misclassification

Table 3-2. Overview of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Cancer

Reference; population	Exposure assessment	Confounders considered	Strengths and limitations[a]
Purdue et al. 2017; Workers (United States)	JEM/JTEM; exposure duration; estimated probability of exposure	Study center; age at reference; race; sex; education; smoking; BMI; history of hypertension	Strengths[b]: obtained detailed information on workplace tasks; assessed occupational exposure to six different chlorinated solvents Limitations[b]: number of highly-exposed participants for each solvent was small; potential for recall and selection bias; low response rate among controls
Ruder et al. 2013; Workers (United States)	JEM; no quantitative exposure	Sex; age; age group; education	Strengths[b]: large number of histologically confirmed gliomas; use of population-based controls; estimation of workplace exposure by industrial hygienists blinded to the case-control status of participants Limitations[b]: lack of detailed information from participants regarding occupational exposures; assumption that workplace exposure levels were within ranges reported in the literature
Saberi Hosnijeh et al. 2013; Workers (Europe)	JEM; semi-quantitative exposure	Age at recruitment; sex; country; smoking status; alcohol intake	Strengths[b]: long follow-up period Limitations[b]: no information on duration of exposure; lack of information on full occupational histories; potential for exposure misclassification
Shu et al. 1999; Children of workers (United States, Canada, and Australia)	JEM; no quantitative exposure	Child's age at diagnosis; sex; year of diagnosis; maternal age and education	Strengths: none reported Limitations: potential misclassification; no description of jobs with possible trichloroethylene exposure; low prevalence of exposure to trichloroethylene limits statistical power
Vlaanderen et al. 2013; Workers (Finland, Iceland, Norway, Sweden)	JEM; estimated cumulative exposure	Sex	Strengths[b]: examined cumulative exposure tertiles based on JEM Limitations[b]: no adjustment for potential confounders; general population had low exposure prevalence; potential for misclassification error from JEM

Table 3-2. Overview of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Cancer

Reference; population	Exposure assessment	Confounders considered	Strengths and limitations[a]
Wang et al. 2009; Workers (United States)	JEM; no quantitative exposure	Age; race; family history of hematopoietic cancers; alcohol consumption	Strengths: validated JEM Limitations: potential for exposure misclassification; low prevalence of high intensity exposure limits statistical power

[a]Unless otherwise noted, study strengths and limitations were noted by EPA (2011e).
[b]Study strengths and limitations were noted by the study authors.

BMI = body mass index; HPV = human papilloma virus; JEM = job-exposure matrix; JTEM = job/task-exposure matrix; NHL = non-Hodgkin's lymphoma; SES = socio-economic status; SOC = socio-occupational category TEM = task-exposure matrix

Exposure assessment methods are listed in Table 3-2. It is important to note that none of the exposure assessments included individual monitoring data or rigorous monitoring of trichloroethylene concentrations in individual workplaces. One pooled case-control study (Cocco et al. 2013), one cohort study (Morgan et al. 1998), and five case-control studies (Charbotel et al. 2006; Christensen et al. 2013; Krishnadasan et al. 2007; Purdue et al. 2011; Saberi-Hosnijeh et al. 2013) provided semi-quantitative estimates of exposure. The remaining studies provided qualitative descriptions of exposure (e.g., exposed/not exposed, probable, substantial, low-moderate-high) based on job-exposure matrices and/or occupational history from union records, census records, and/or participant questionnaires. Exposure conditions most likely differ widely between study populations (e.g., exposure levels, peak exposures), which could explain different study outcomes. For most study participants, it is likely that exposure included other solvents or chemicals.

The potential influence of confounding factors is an important consideration in the interpretation of these epidemiological studies. As shown in Table 3-2, confounders were not consistently addressed across studies. Most studies adjusted risk estimates for age, sex, and race. Studies by Christensen et al. (2013), Neta et al. (2012), and Silver et al. (2014) provided the most comprehensive assessment of confounders, and other studies considered several confounders (Dosemeci et al. 1999; Dumas et al. 2000; Krishnadasan et al. 2007; Mattei et al. 2014). For carcinogenicity assessments of trichloroethylene, it is important to consider the potential influence of exposure to other solvents and chemicals (EPA 2012a). However, relatively few studies considered smoking status (Brüning et al. 2003; Charbotel et al. 2006; Dosemeci et al. 1999; Dumas et al. 2000; Mattei et al. 2014; Neta et al. 2012; Pesch et al. 2000; Purdue et al. 2017; Saberi-Hosnijeh et al. 2013) or concomitant exposure to other chemicals (Boice et al. 2006; Christensen et al. 2013; Hadkhale et al. 2017; Krishnadasan et al. 2007; Mattei et al. 2014; Neta et al. 2012; Silver et al. 2014). Only one study considered family history of cancers as a confounding factor (Wang et al. 2009). One study did not list any confounding factors (Buhagen et al. 2016).

Study results based on cancer type are shown in the following figures: kidney cancer (Figure 3-2); non-Hodgkin's lymphoma (Figure 3-3); liver cancer (Figure 3-4); esophageal cancer (Figure 3-5); stomach cancer (Figure 3-6); colorectal cancer (Figure 3-7); bladder cancer (Figure 3-8); pancreatic cancer (Figure 3-9); lung cancer (Figure 3-10); breast cancer (Figure 3-11); female reproductive cancer (Figure 3-12); male reproductive cancer (Figure 3-13); central nervous system cancer (Figure 3-14); multiple myeloma (Figure 3-15); and leukemia (Figure 3-16).

Figure 3-2. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Kidney Cancer

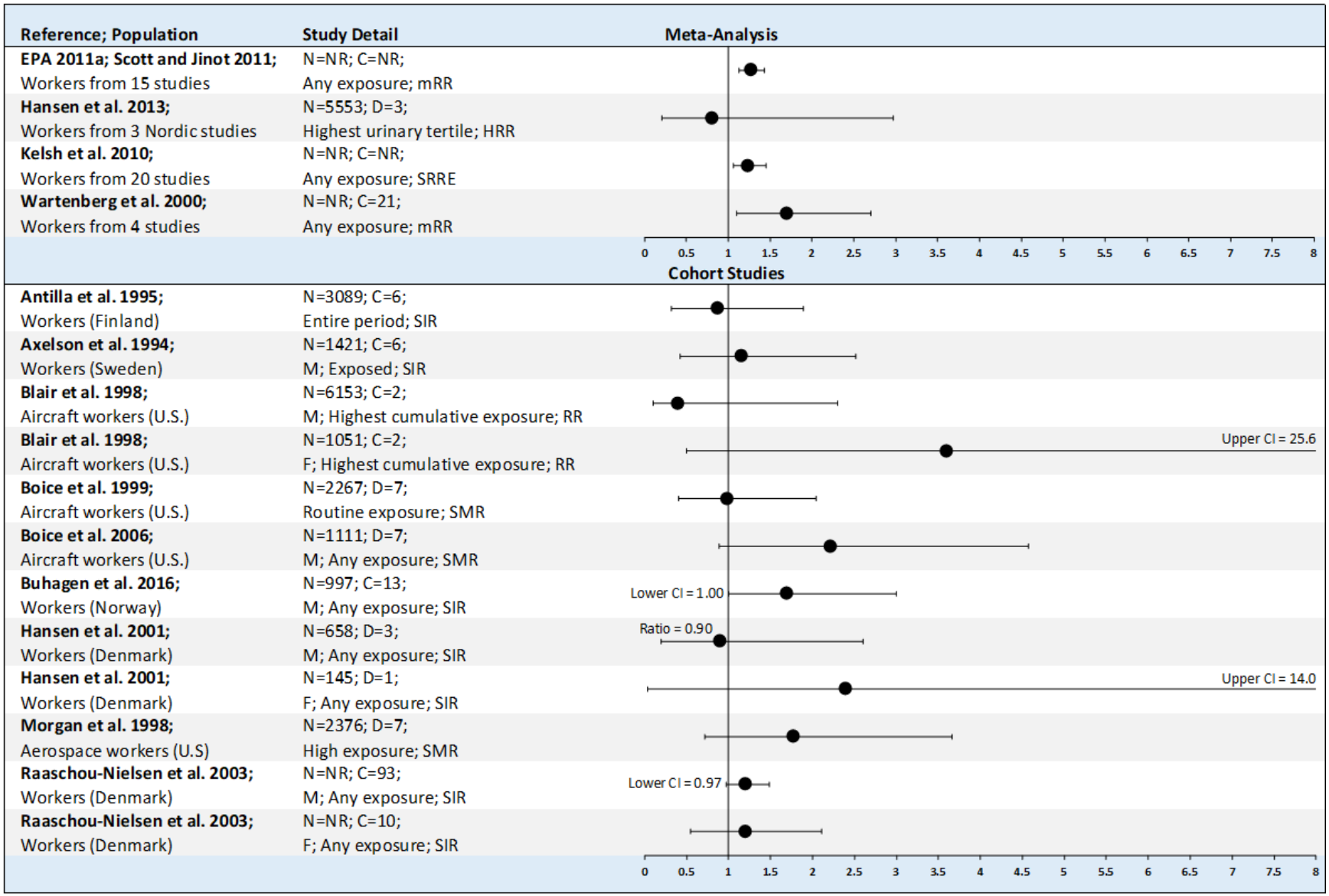
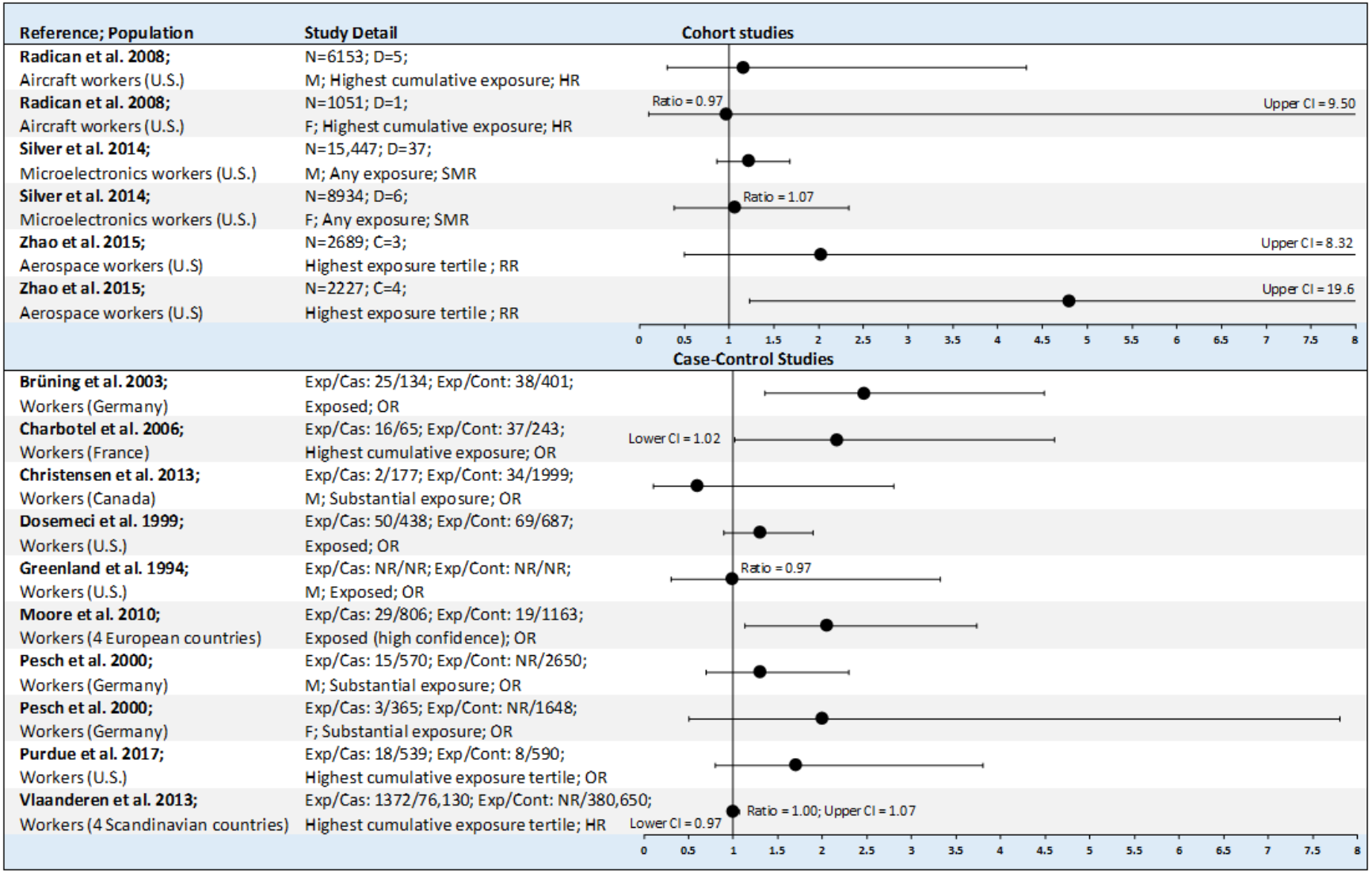


Figure 3-2 *(continued)*. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Kidney Cancer



—●— = risk estimate and 95% CI

C = number with kidney cancer; CI = confidence interval; D = number of deaths due to kidney cancer; Exp/Cas = number of exposed cases/number of cases; Exp/Cont = number of exposed controls/number of controls; F = females; HR = hazard ratio; M = males; mRR = meta relative risk; N = number of participants; NR = not reported; OR = odds ratio; RR = rate ratio; SIR = standardized incidence ratio; SMR = standardized mortality ratio; SRRE = summary relative risk estimate

Figure 3-3. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Non-Hodgkin's Lymphoma

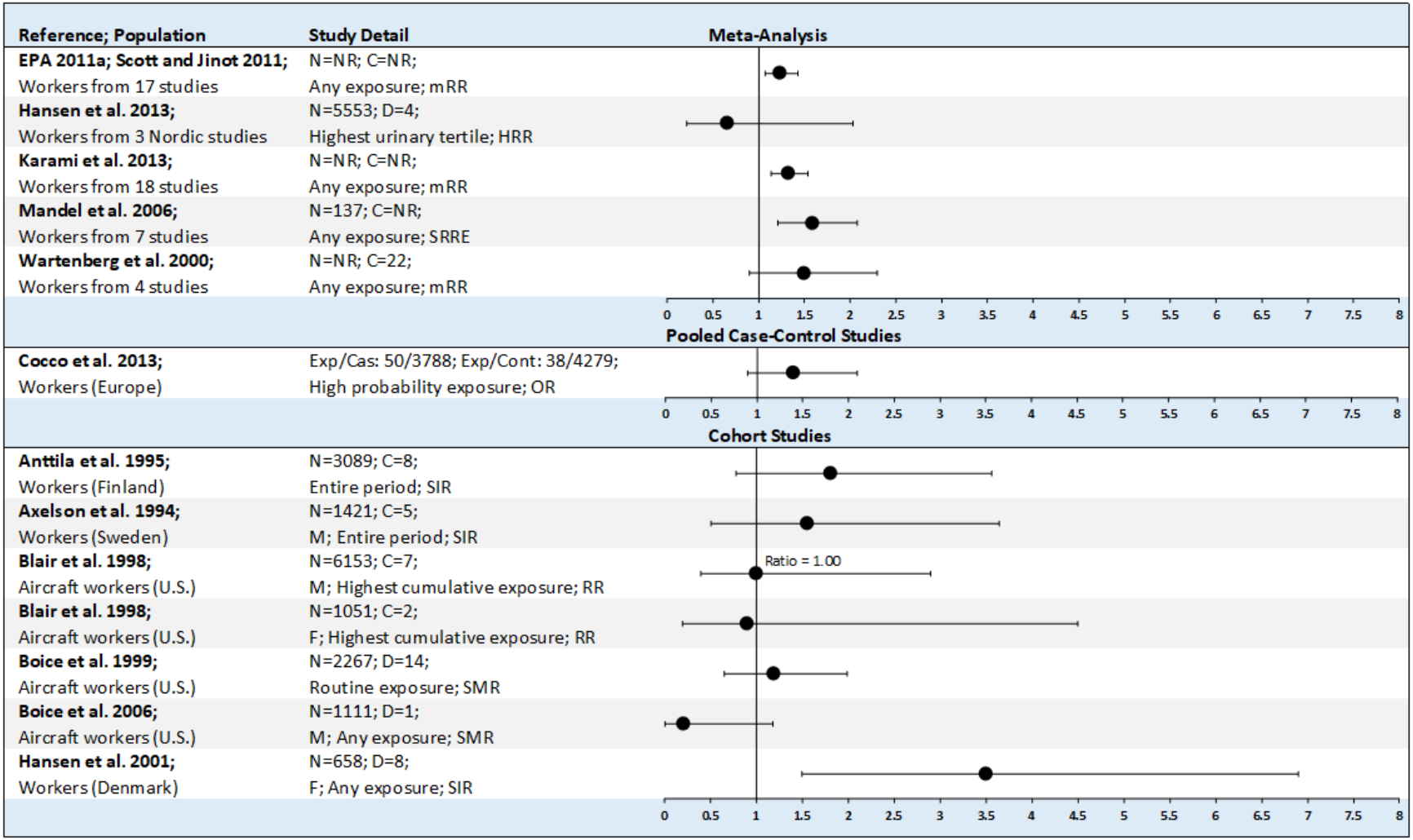
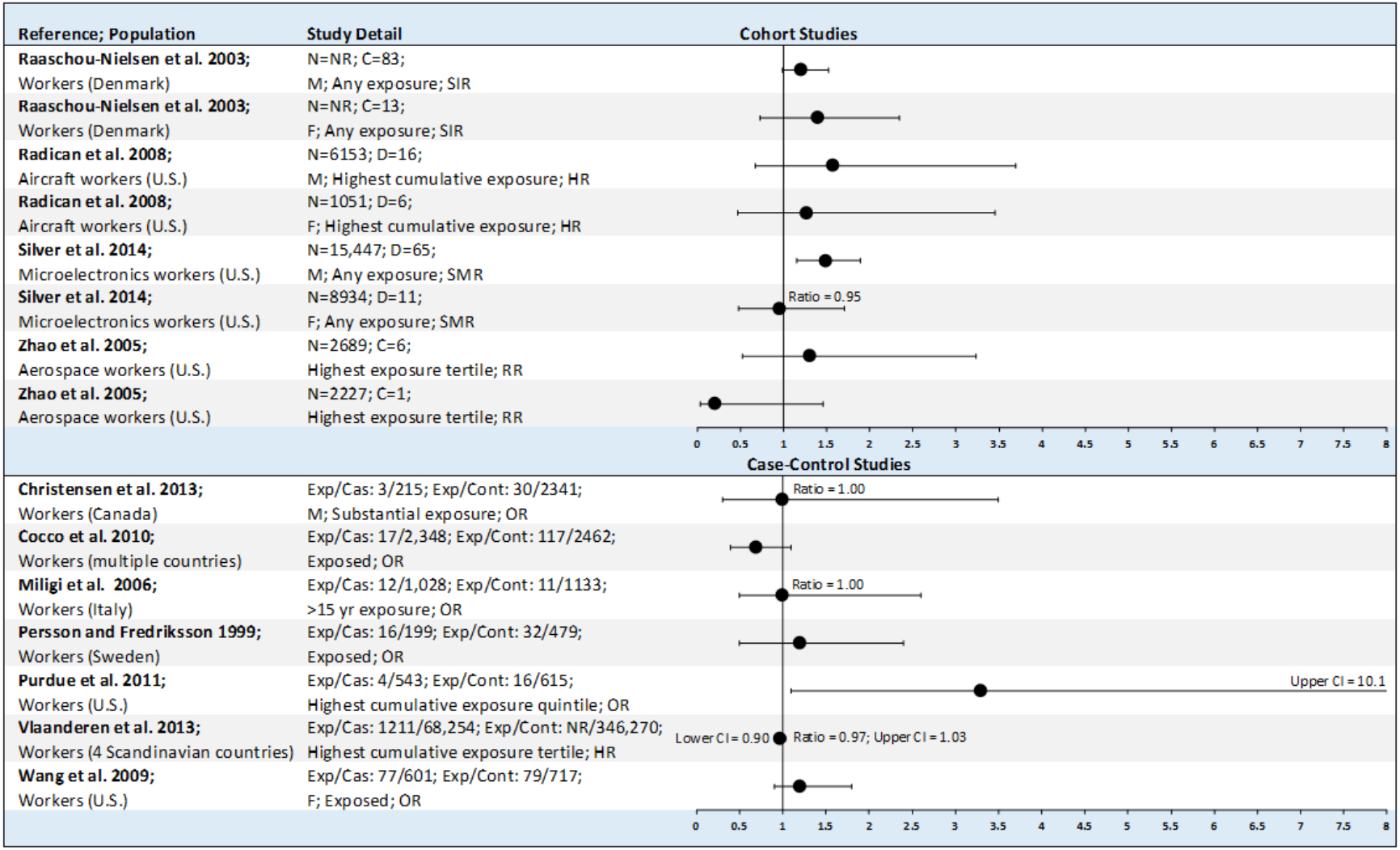


Figure 3-3 *(continued)*. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Non-Hodgkin's Lymphoma



—●— = risk estimate and 95% CI

C = number with non-Hodgkin's lymphoma; CI = confidence interval; D = number of deaths due to non-Hodgkin's lymphoma; Exp/Cas = number of exposed cases/number of cases; Exp/Cont = number of exposed controls/number of controls; F = females; HR = hazard ratio; M = males; mRR = relative risk ratio; N = number of participants; NR = not reported; OR = odds ratio; RR = rate ratio; SIR = standardized incidence ratio; SMR = standardized mortality ratio; SRRE = summary relative risk estimate; yr = year

Figure 3-4. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Liver Cancer

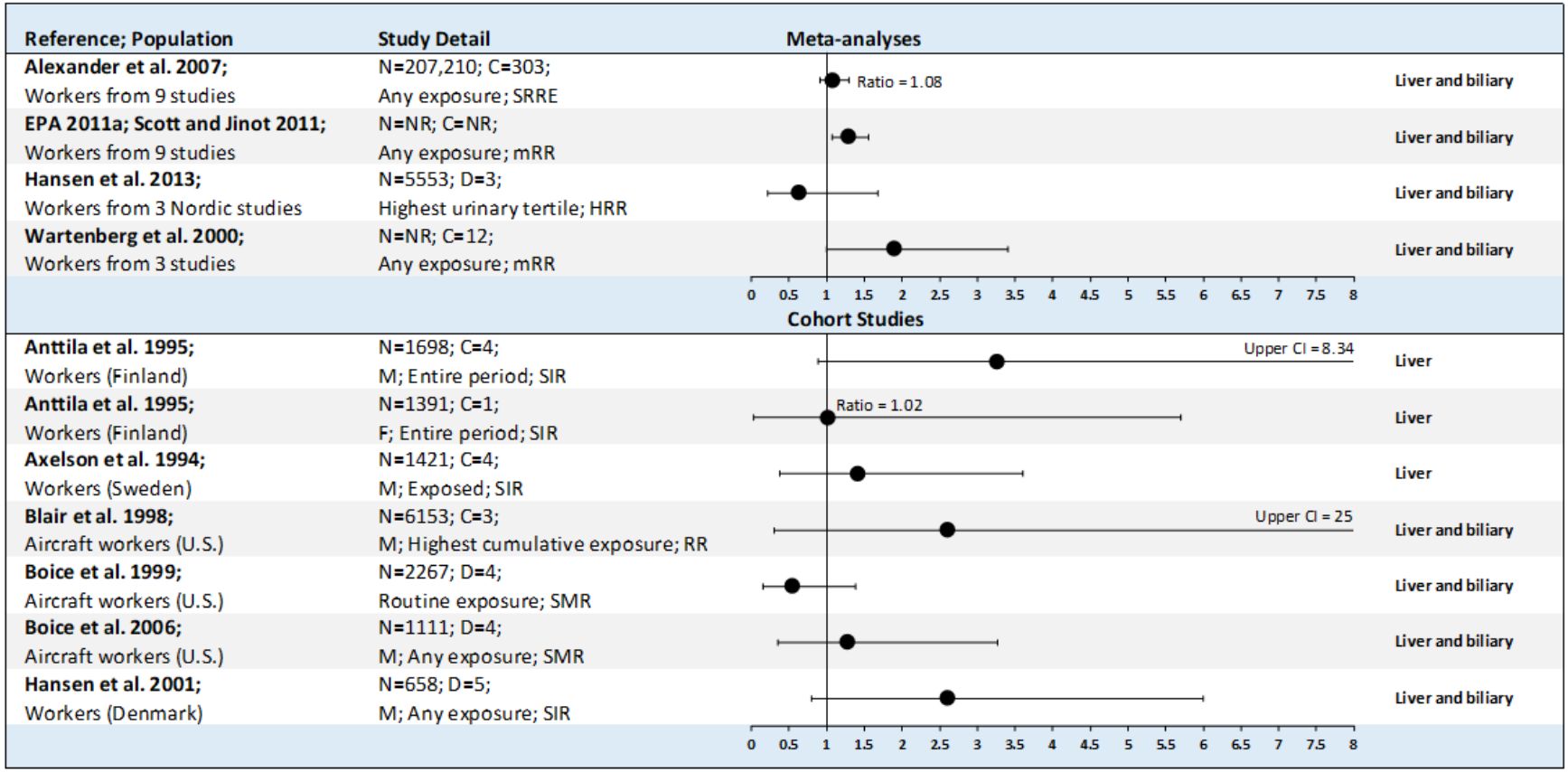
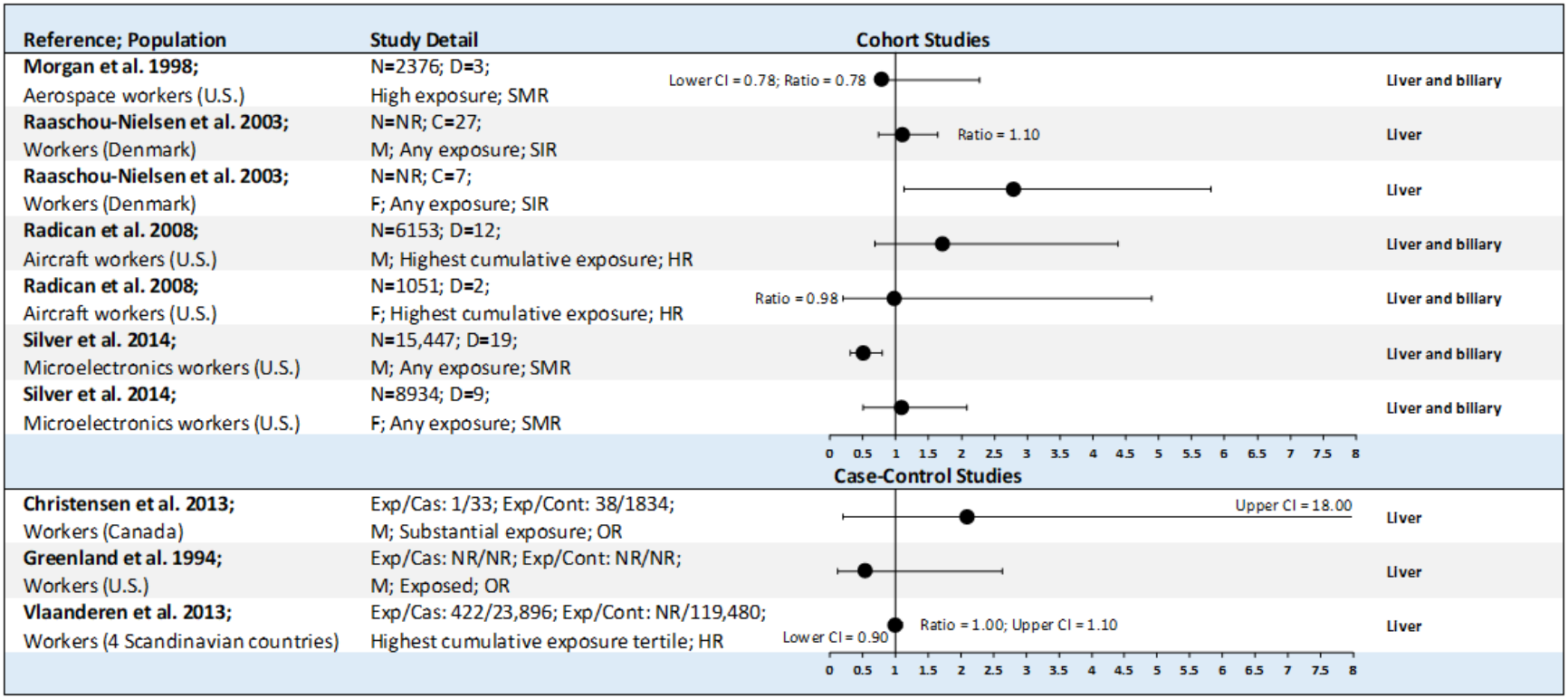


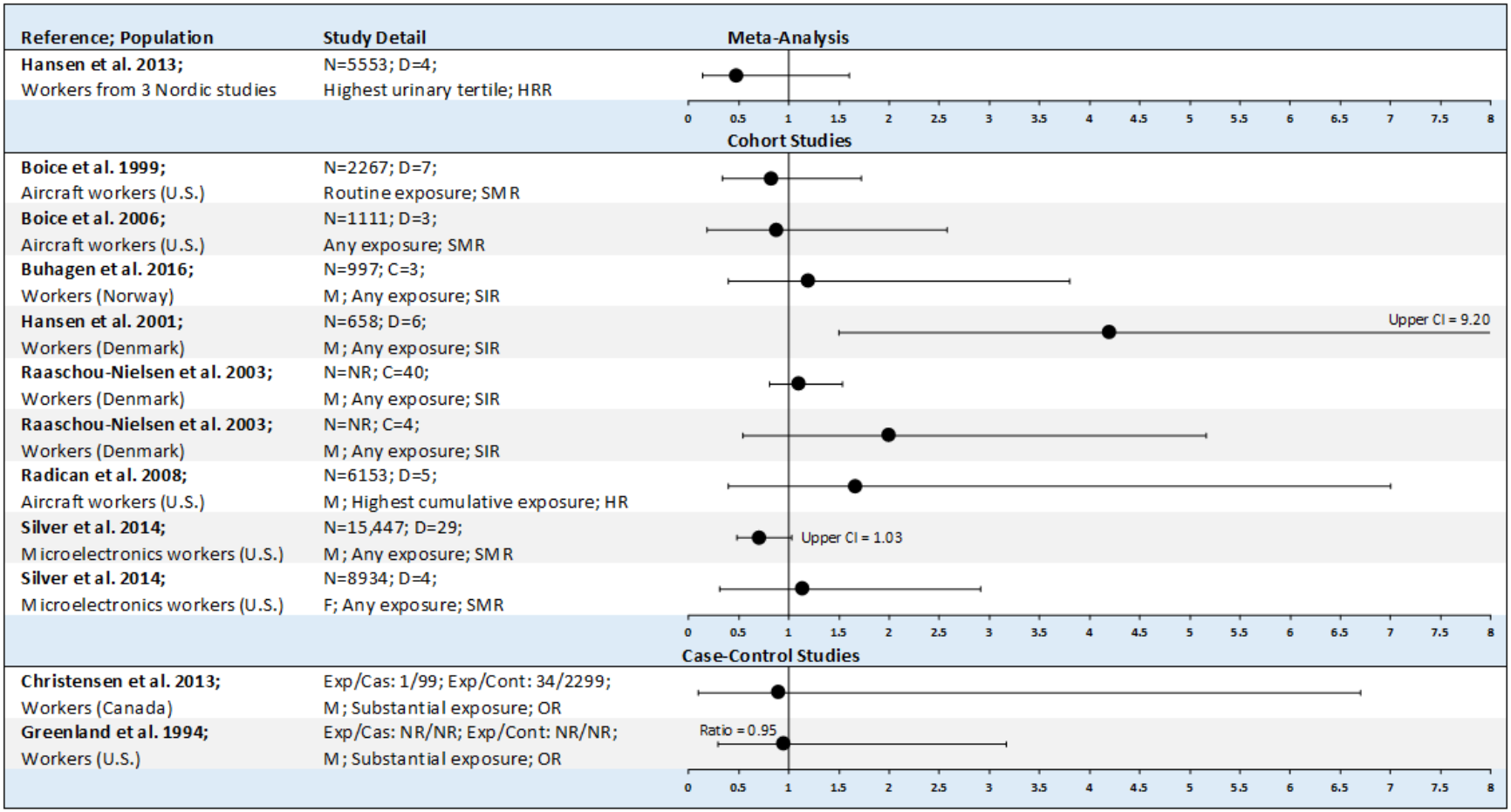
Figure 3-4 *(continued)*. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Liver Cancer



= risk estimate and 95% CI

C = number with liver cancer; CI = confidence interval; D = number of deaths due to liver cancer; Exp/Cas = number of exposed cases/number of cases; Exp/Cont = number of exposed controls/number of controls; F = females; HR = hazard ratio; M = males; mRR = meta relative risk; N = number of participants; NR = not reported; OR = odds ratio; RR = rate ratio; SIR = standardized incidence ratio; SMR = standardized mortality ratio; SRRE = summary relative risk estimate

Figure 3-5. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Esophageal Cancer



= risk estimate and 95% CI

C = number with esophageal cancer; CI = confidence interval; D = number of deaths due to esophagael cancer; Exp/Cas = number of exposed cases/number of cases; Exp/Cont = number of exposed controls/number of controls; F = females; HR = hazard ratio; M = males; N = number of participants; NR = not reported; OR = odds ratio; SIR = standardized incidence ratio; SMR = standardized mortality ratio

Figure 3-6. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Stomach Cancer[a]

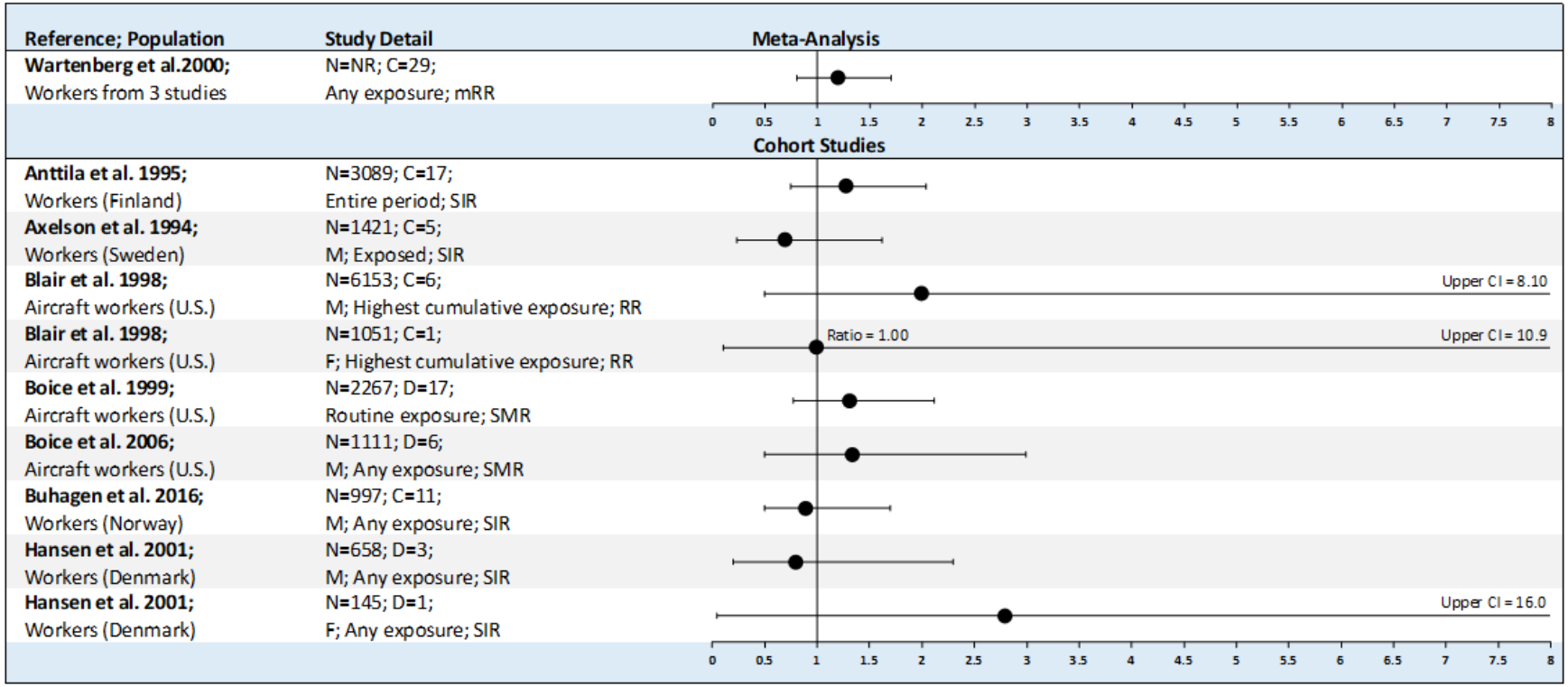
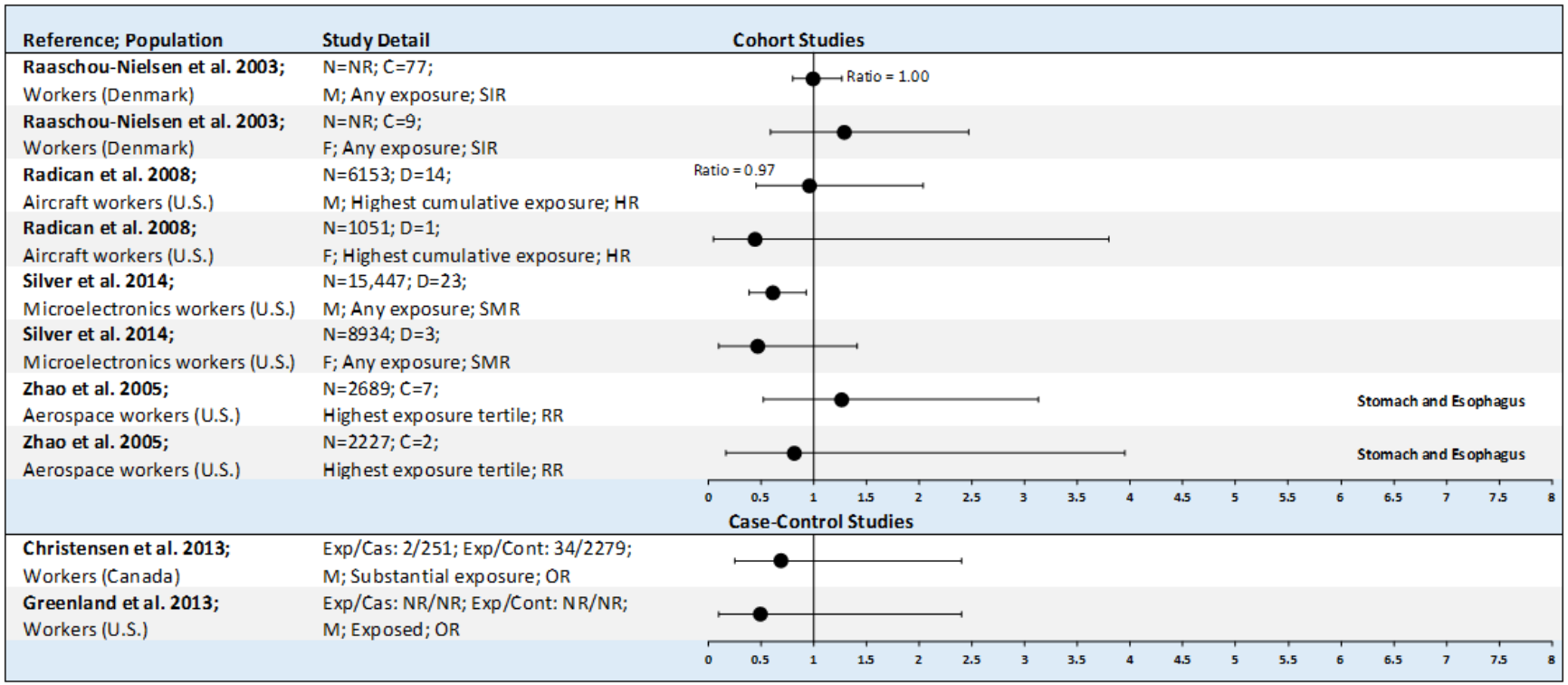


Figure 3-6 *(continued)*. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Stomach Cancer[a]



[a]Unless otherwise noted, risk estimates are for stomach cancer only

⊢●⊣ = risk estimate and 95% CI

C = number with stomach cancer; CI = confidence interval; D = number of deaths due to stomach cancer; Exp/Cas = number of exposed cases/number of cases; Exp/Cont = number of exposed controls/number of controls; F = females; HR = hazard ratio; M = males; mRR = meta relative risk; N = number of participants; NR = not reported; OR = odds ratio; RR = rate ratio; SIR = standardized incidence ratio; SMR = standardized mortality ratio

Figure 3-7. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Colorectal Cancer

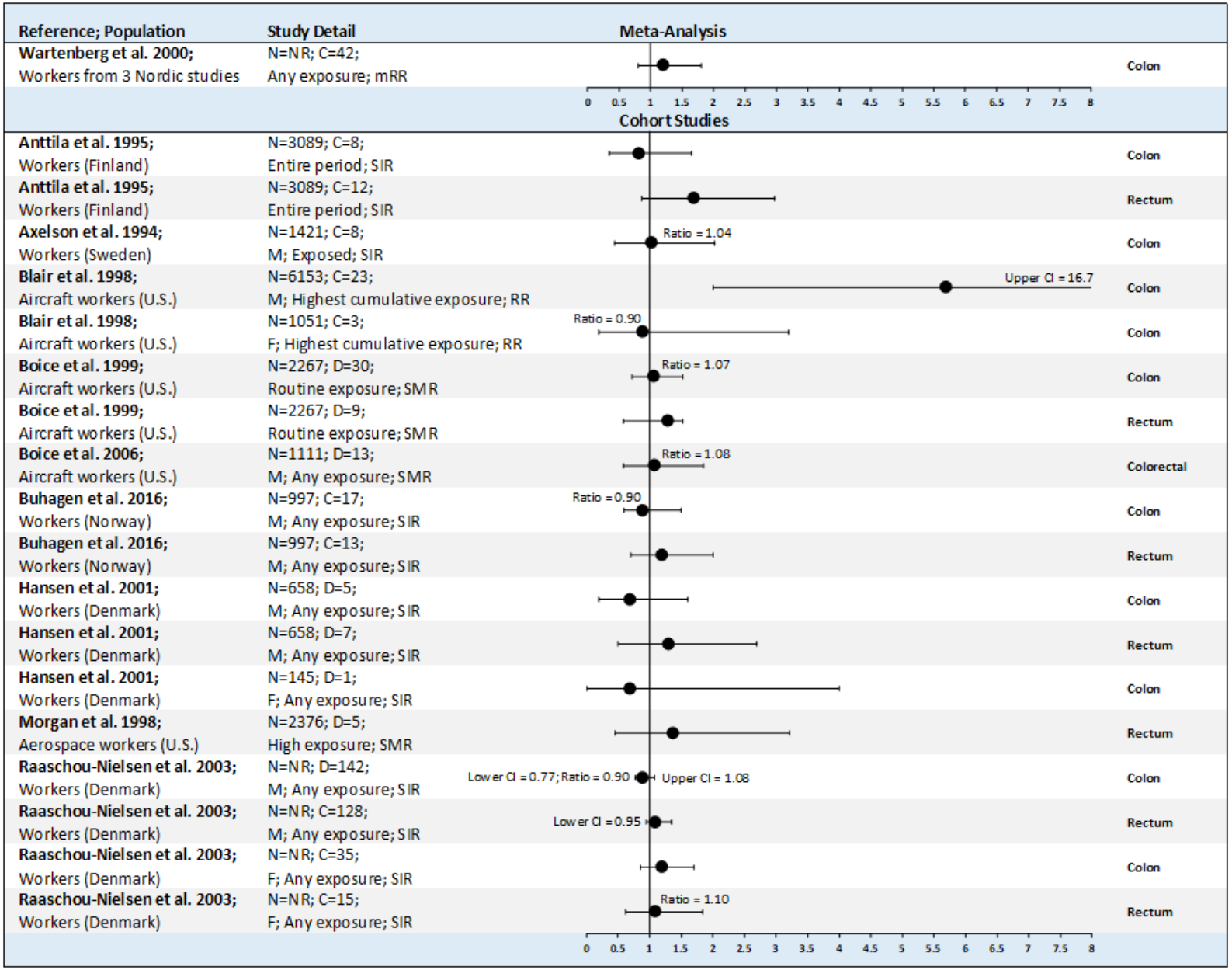
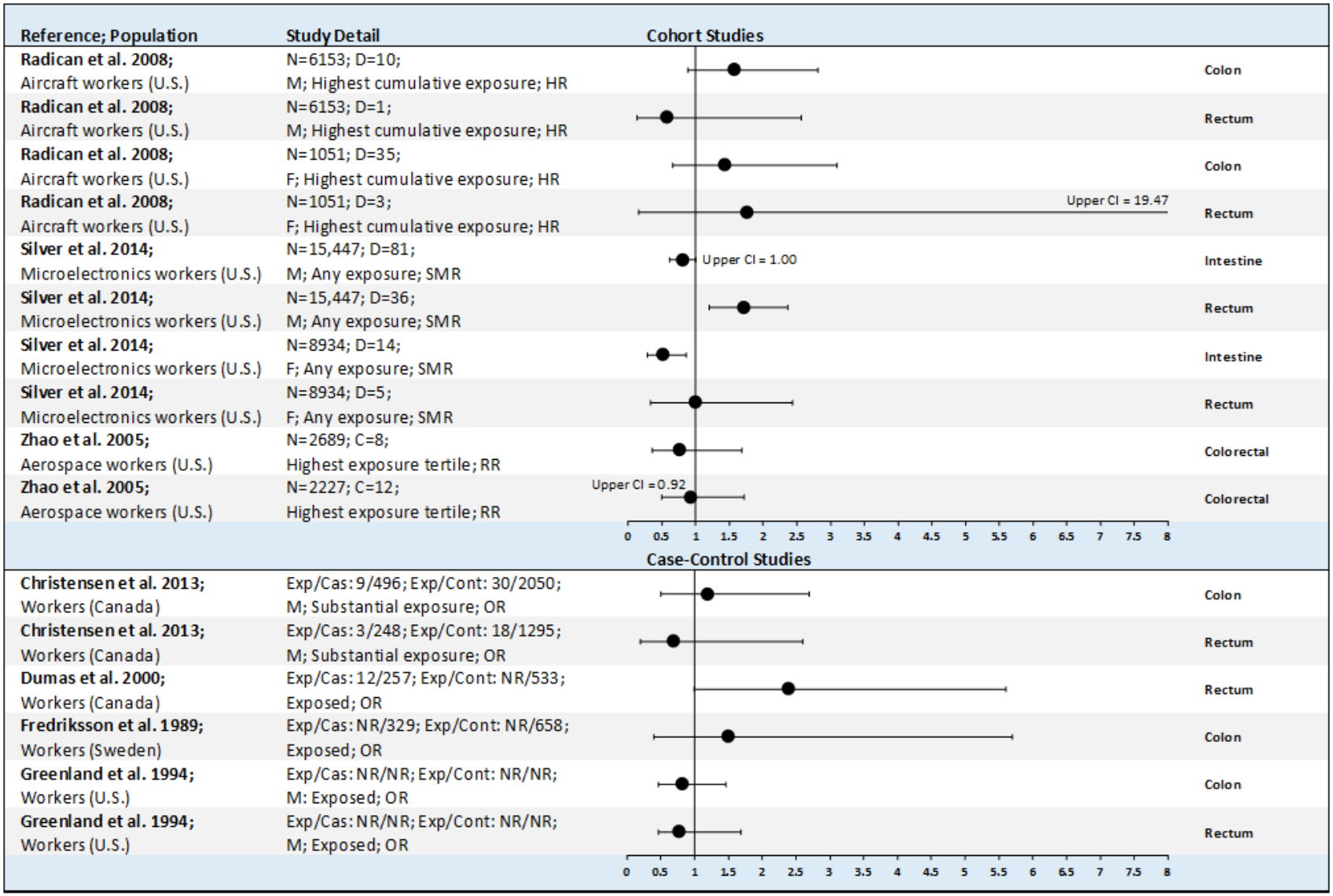


Figure 3-7 *(continued)*. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Colorectal Cancer



= risk estimate and 95% CI

C = number with colorectal cancer; CI = confidence interval; D = number of deaths due to colorectal cancer; Exp/Cas = number of exposed cases/number of cases; Exp/Cont = number of exposed controls/number of controls; F = females; HR = hazard ratio; M = males; mRR = relative risk ratio; N = number of participants; NR = not reported; OR = odds ratio; RR = rate ratio; SIR = standardized incidence ratio; SMR = standardized mortality ratio

Figure 3-8. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Bladder Cancer

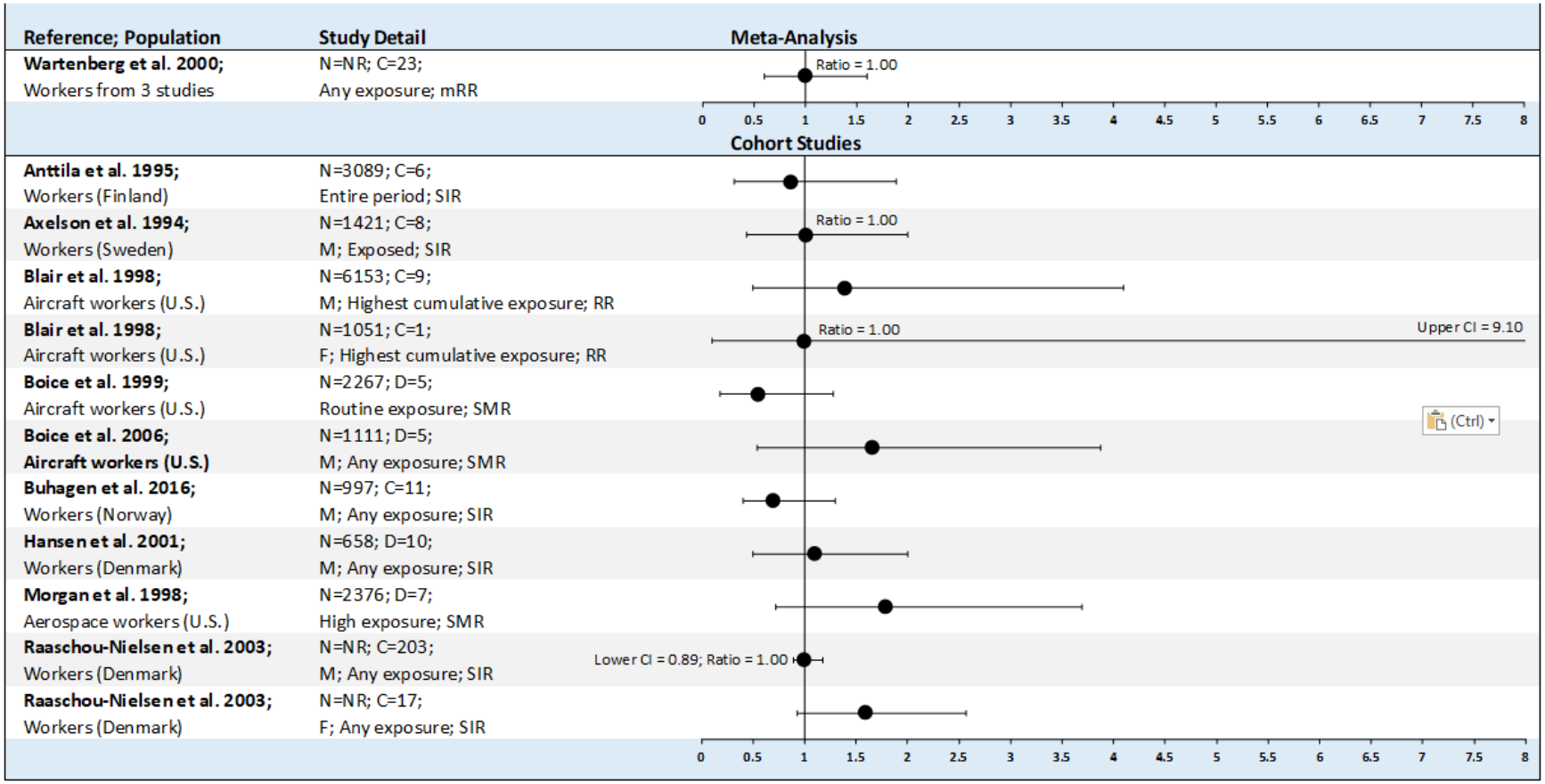
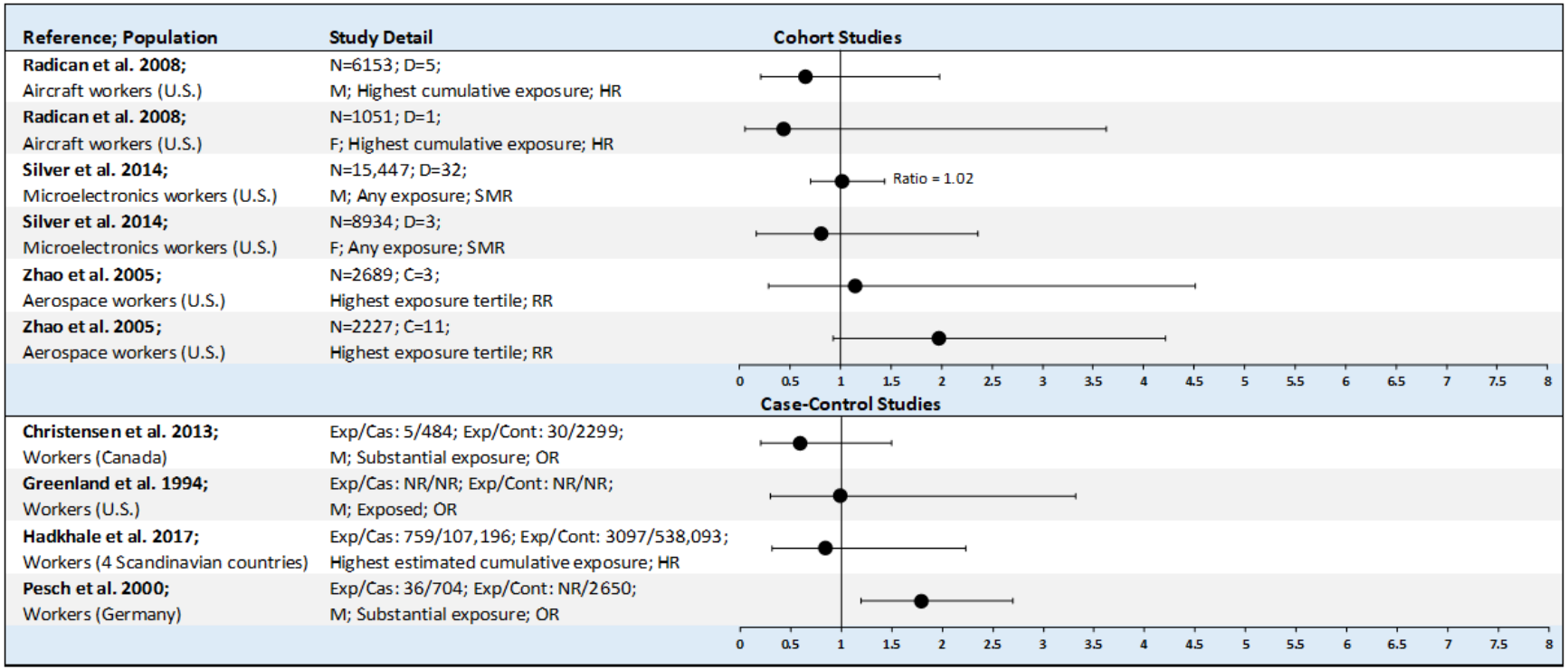


Figure 3-8 *(continued)*. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Bladder Cancer



—●— = risk estimate and 95% CI

C = number with bladder cancer; CI = confidence interval; D = number of deaths due to bladder cancer; Exp/Cas = number of exposed cases/number of cases; Exp/Cont = number of exposed controls/number of controls; F = females; HR = hazard ratio; M = males; mRR = meta relative risk; N = number of participants; NR = not reported; OR = odds ratio; RR = rate ratio; SIR = standardized incidence ratio; SMR = standardized mortality ratio

Figure 3-9. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Pancreatic Cancer

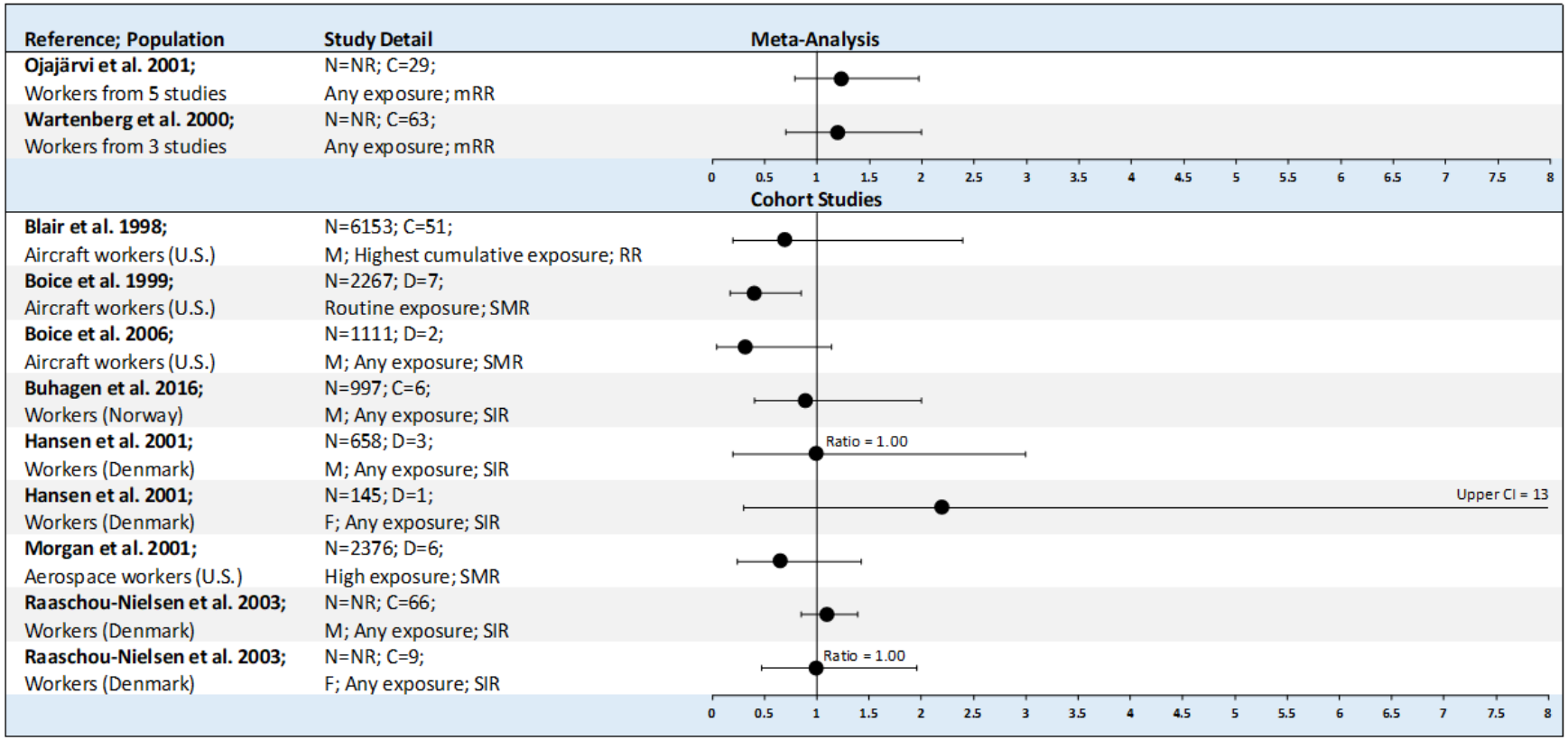
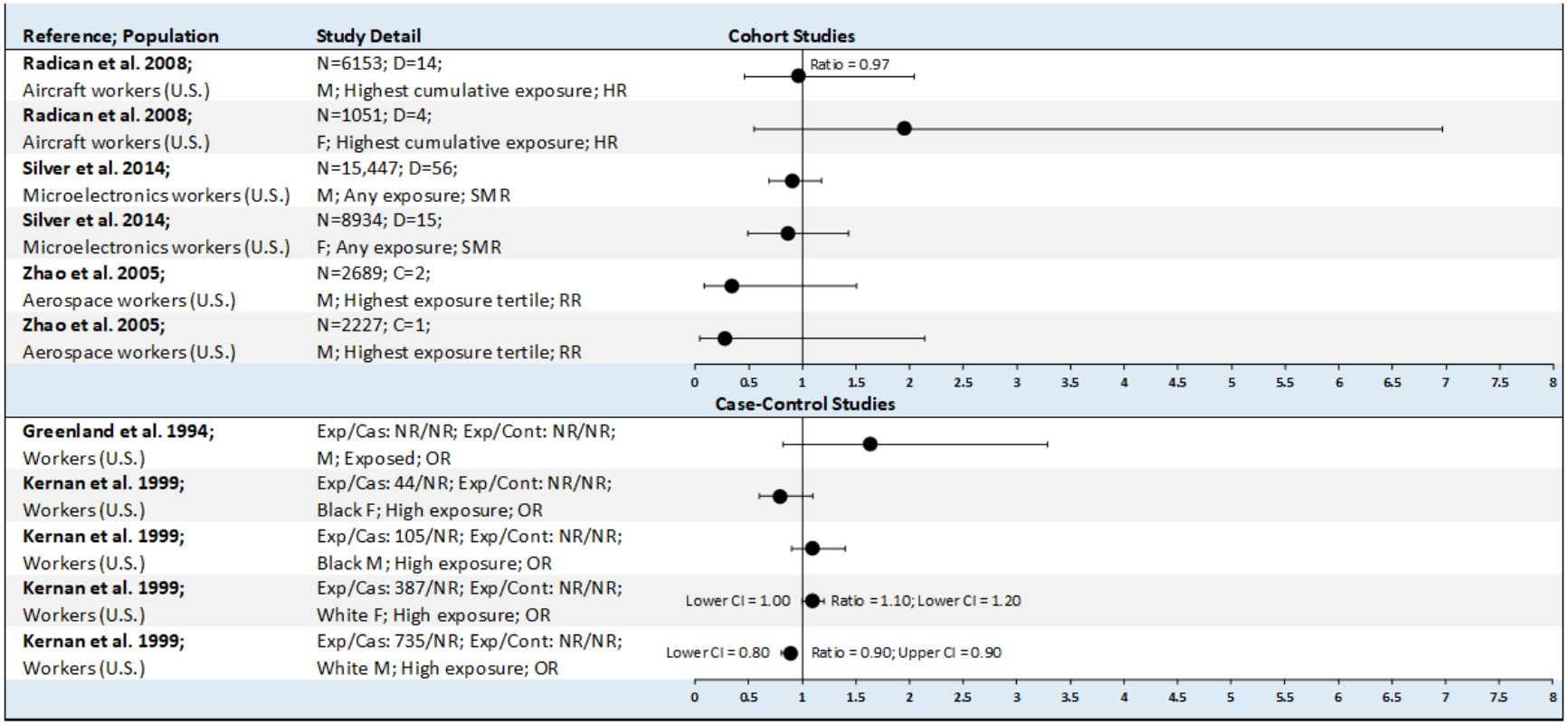


Figure 3-9 *(continued)*. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Pancreatic Cancer



= risk estimate and 95% CI

C = number with pancreatic cancer; CI = confidence interval; D = number of deaths due to pancreatic cancer; Exp/Cas = number of exposed cases/number of cases; Exp/Cont = number of exposed controls/number of controls; F = females; HR = hazard ratio; M = males; mRR = meta relative risk; N = number of participants; NR = not reported; OR = odds ratio; RR = rate ratio; SIR = standardized incidence ratio; SMR = standardized mortality ratio

Figure 3-10. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Lung Cancer

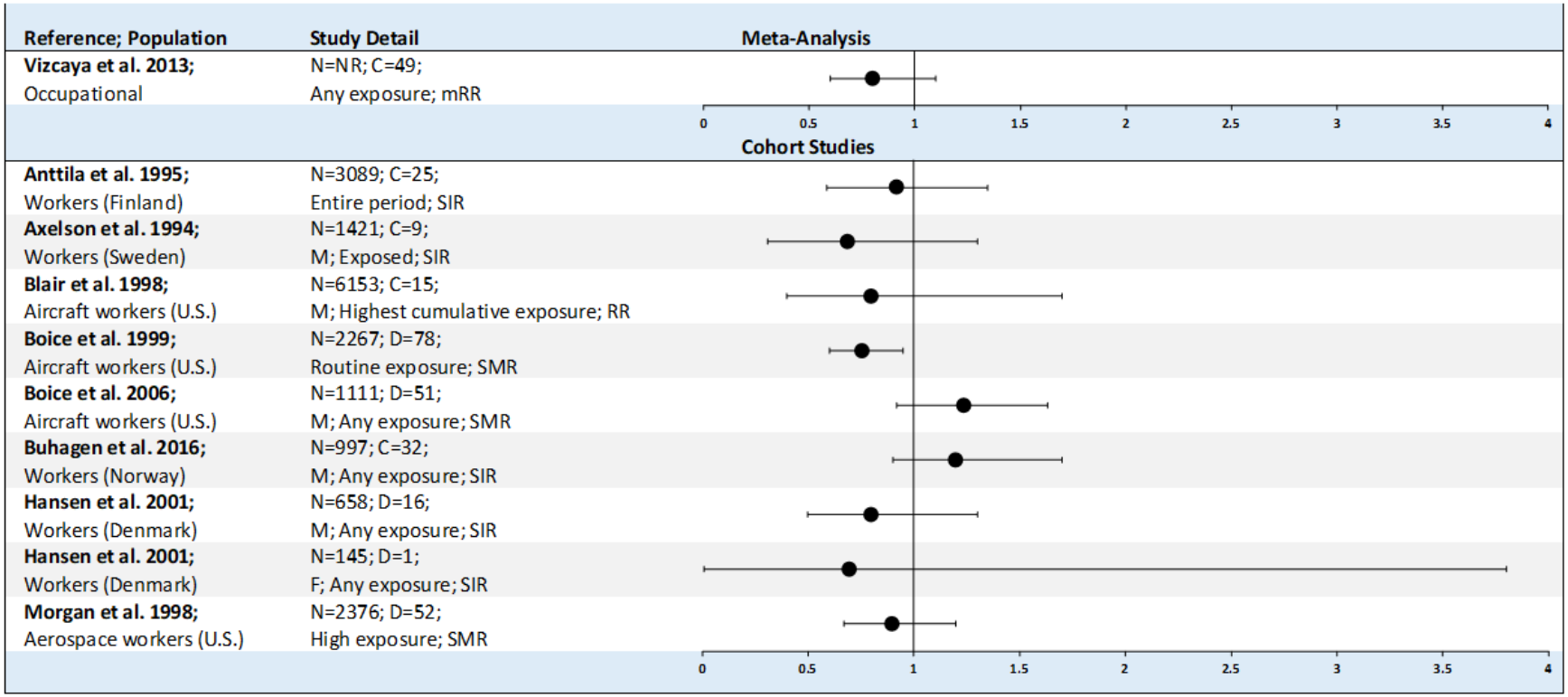
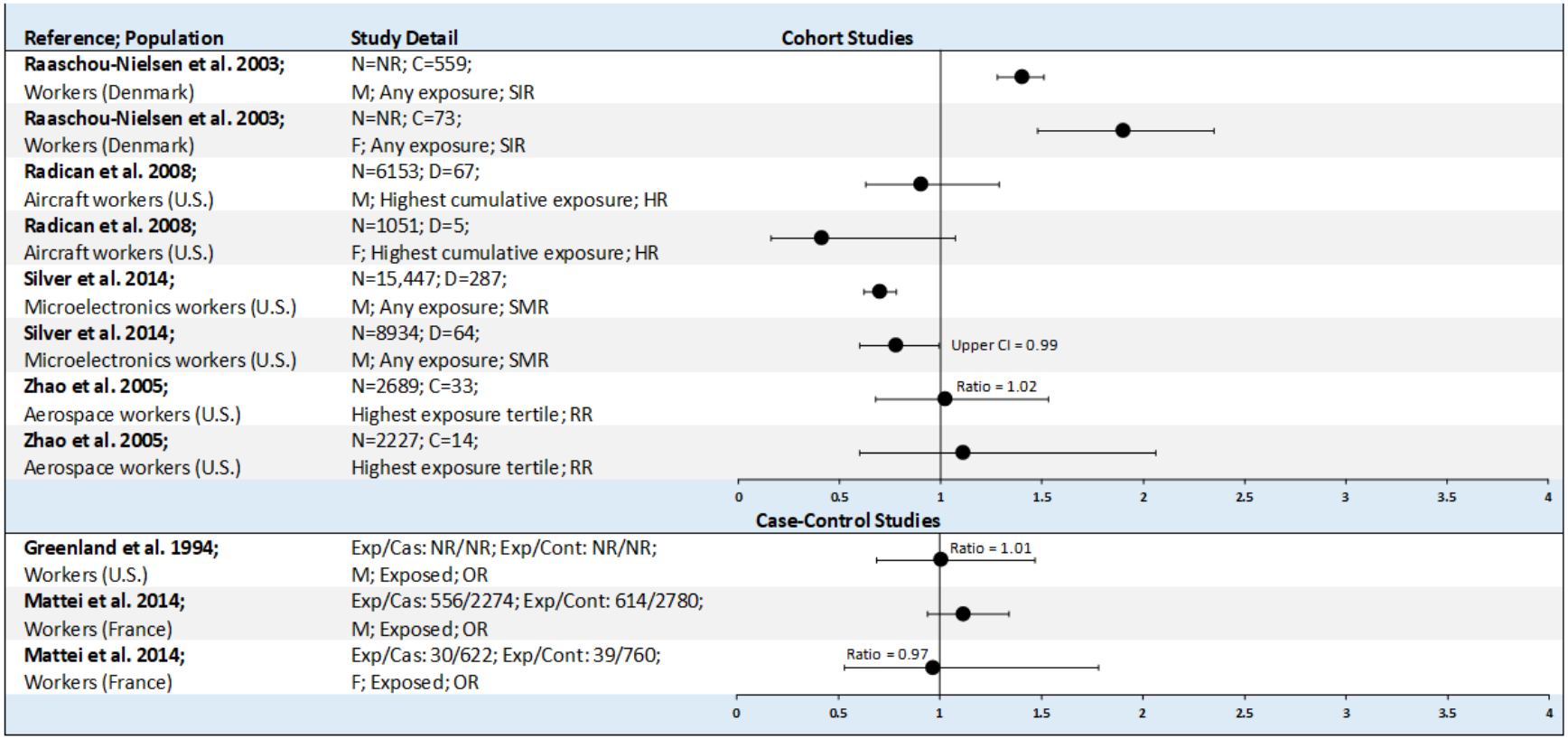


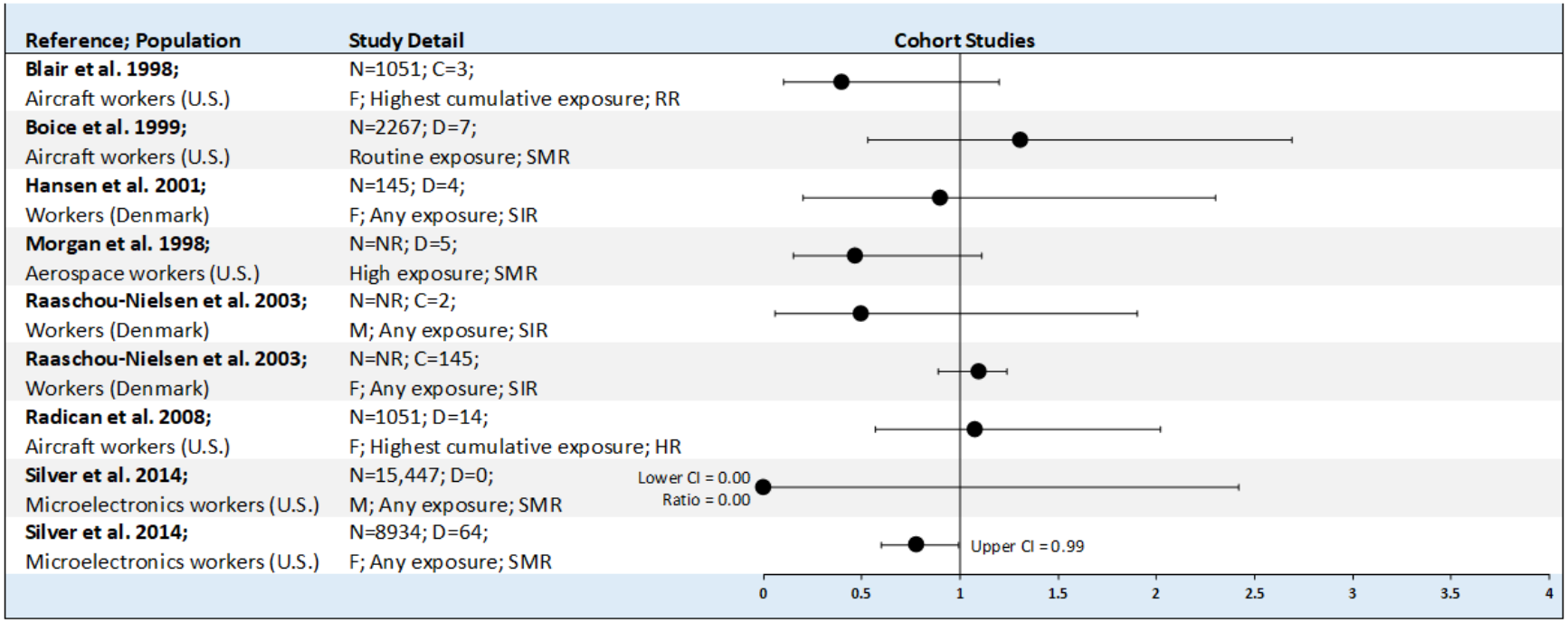
Figure 3-10 *(continued)*. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Lung Cancer



—●— = risk estimate and 95% CI

C = number with lung cancer; CI = confidence interval; D = number of deaths due to lung cancer; Exp/Cas = number of exposed cases/number of cases; Exp/Cont = number of exposed controls/number of controls; F = females; HR = hazard ratio; M = males; mRR = relative risk ratio; N = number of participants; NR = not reported; OR = odds ratio; RR = rate ratio; SIR = standardized incidence ratio; SMR = standardized mortality ratio

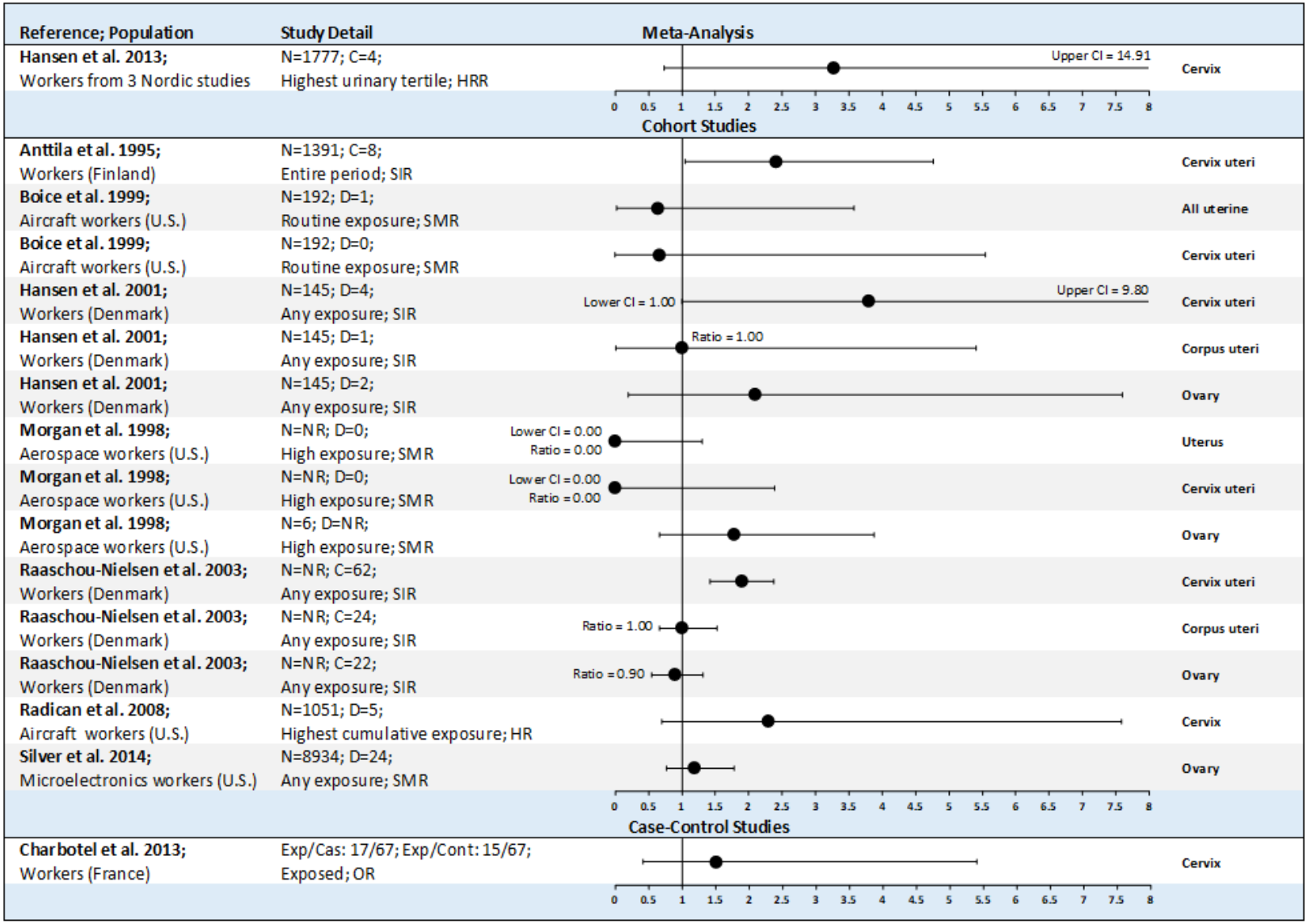
Figure 3-11. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Breast Cancer



= risk estimate and 95% CI

C = number with breast cancer; CI = confidence interval; D = number of deaths due to breast cancer; F = females; HR = hazard ratio; M = males; N = number of participants; NR = not reported; RR = rate ratio; SIR = standardized incidence ratio; SMR = standardized mortality ratio

Figure 3-12. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Female Reproductive Cancer



—●— = risk estimate and 95% CI

C = number with reproductive cancer; CI = confidence interval; D = number of deaths due to female reproductive cancer; Exp/Cas = number of exposed cases/number of cases; Exp/Cont = number of exposed controls/number of controls; HR = hazard ratio; N = number of participants; NR = not reported; OR = odds ratio; SIR = standardized incidence ratio; SMR = standardized mortality ratio

Figure 3-13. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Male Reproductive Cancer

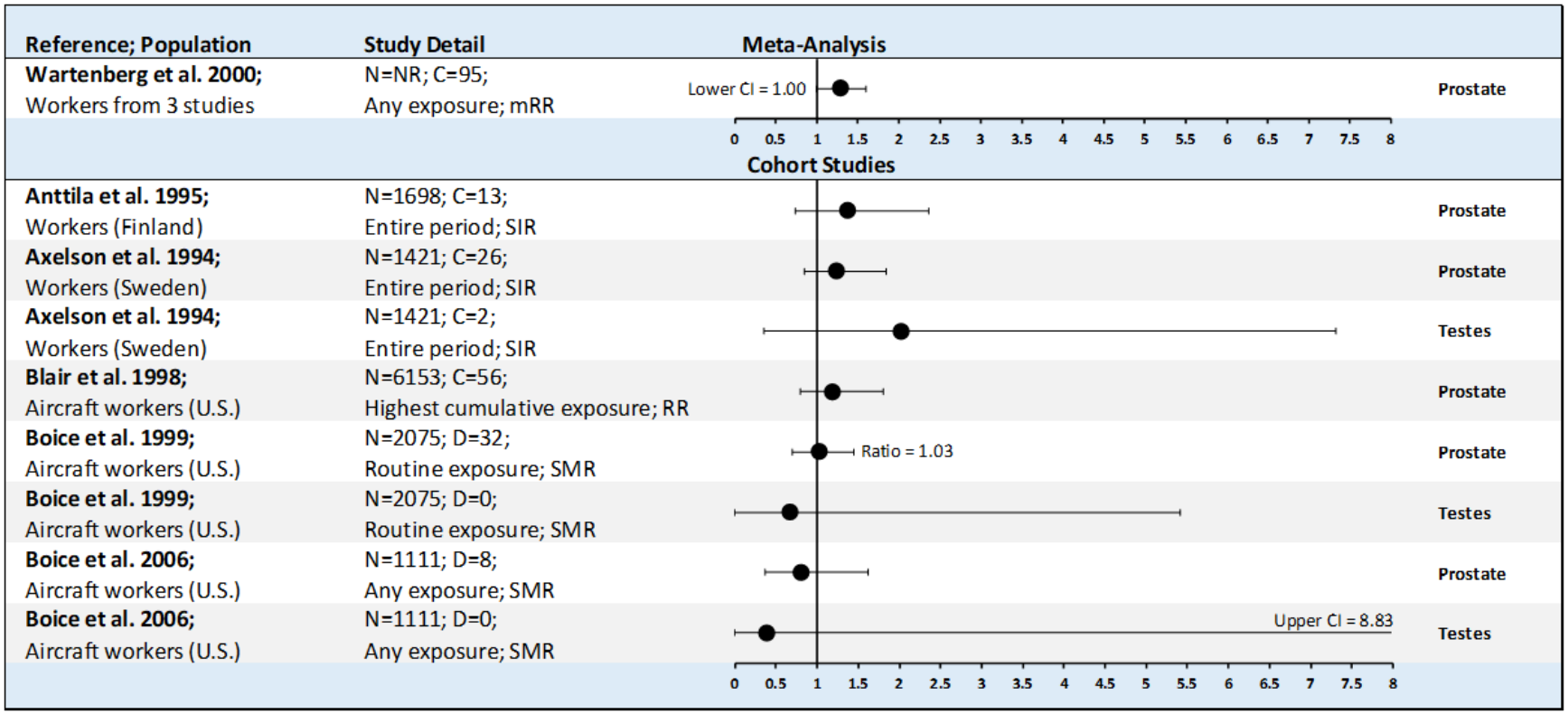
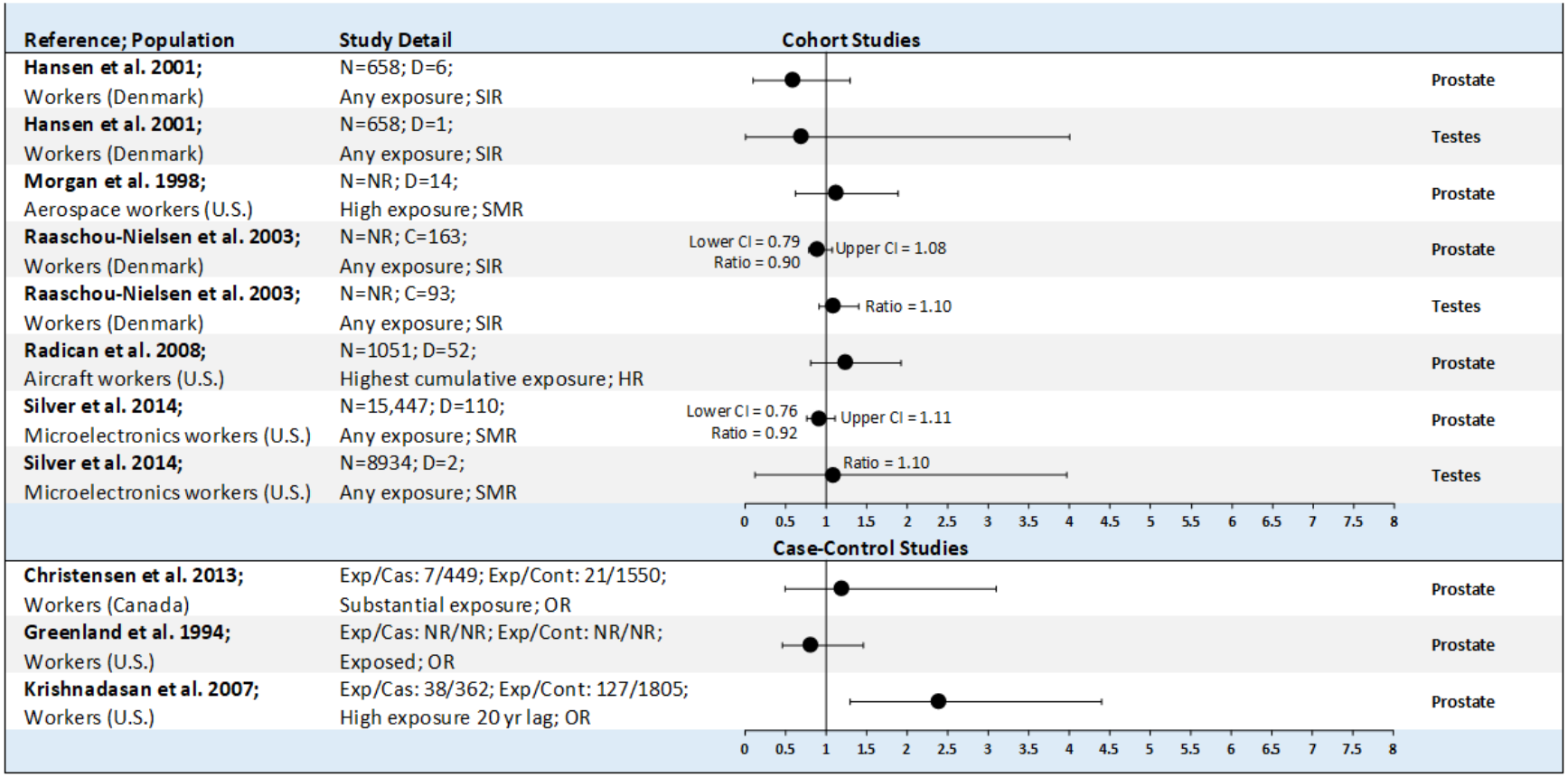


Figure 3-13 *(continued)*. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Male Reproductive Cancer



⊢●⊣ = risk estimate and 95% CI

C = number with reproductive cancer; CI = confidence interval; D = number of deaths due to male reproductive cancer; Exp/Cas = number of exposed cases/number of cases; Exp/Cont = number of exposed controls/number of controls; HR = hazard ratio; mRR = relative risk ratio; N = number of participants; OR = odds ratio; RR = rate ratio; SIR = standardized incidence ratio; SMR = standardized mortality ratio; yr = year

Figure 3-14. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Central Nervous System Cancer

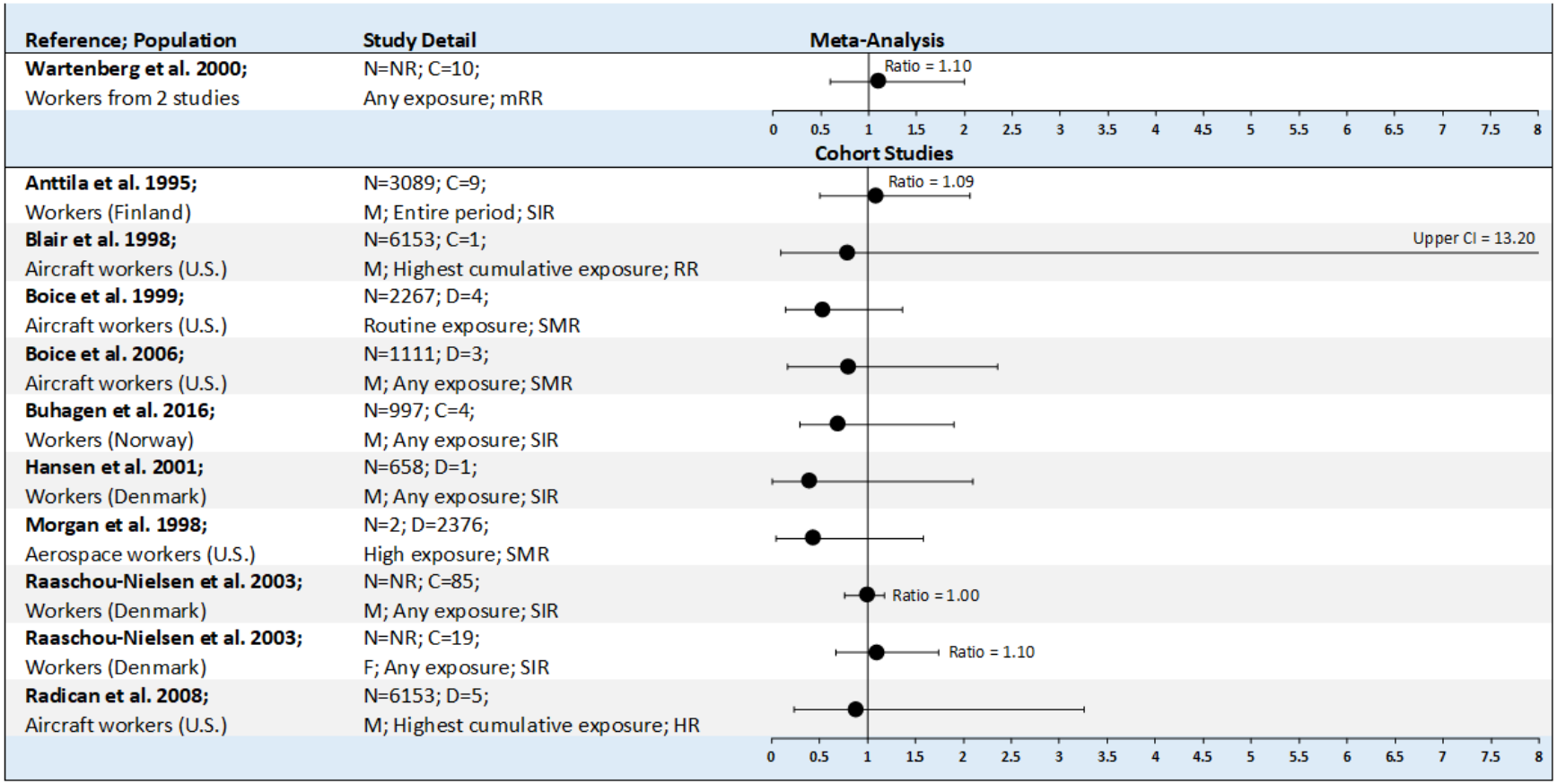
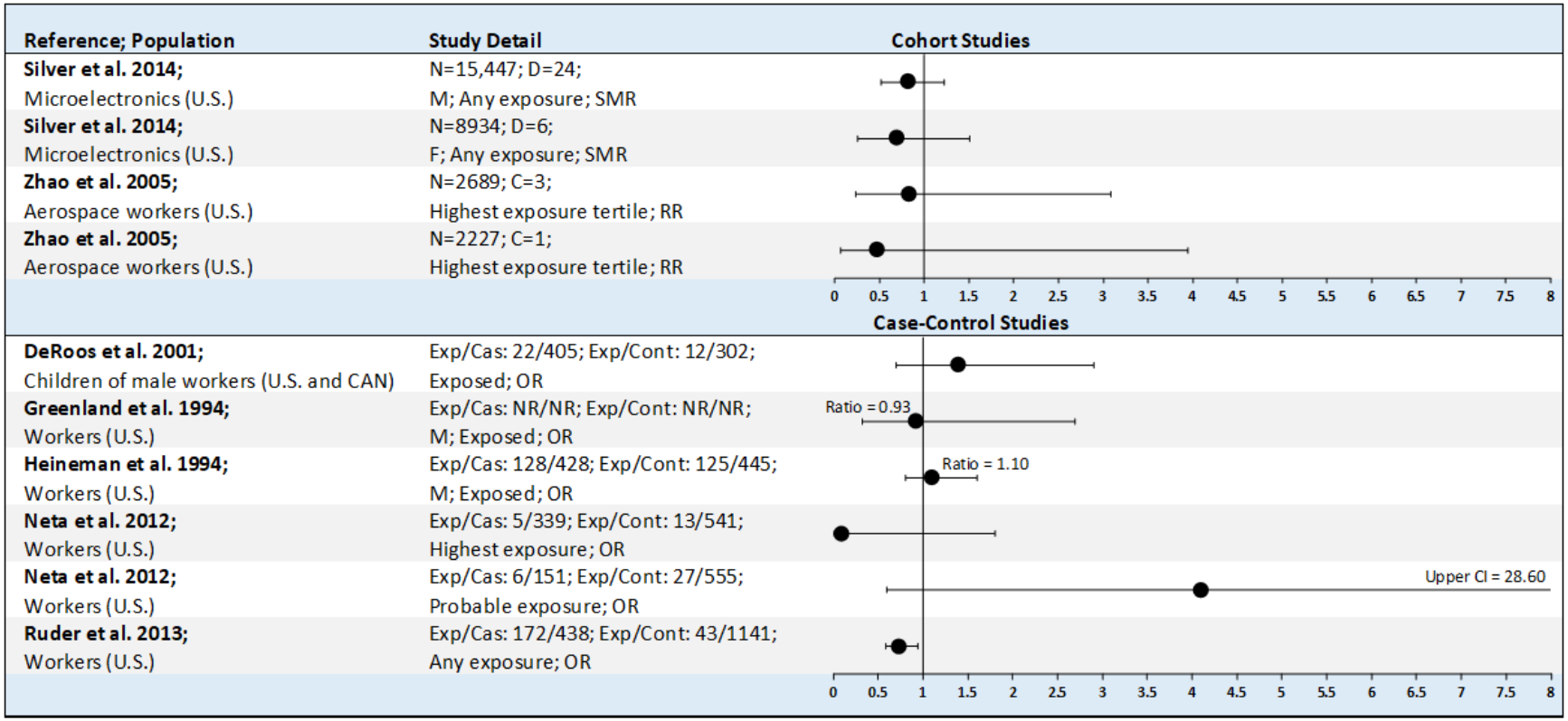


Figure 3-14 *(continued)*. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Central Nervous System Cancer



= risk estimate and 95% CI

C = number with central nervous system cancer; CAN = Canada; CI = confidence interval; CNS = central nervous system; D = number of deaths due to central nervous system cancer; Exp/Cas = number of exposed cases/number of cases; Exp/Cont = number of exposed controls/number of controls; F = females; M = males; N = number of participants; NR = not reported; OR = odds ratio; RR = rate ratio; SMR = standardized mortality ratio

Figure 3-15. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Multiple Myeloma

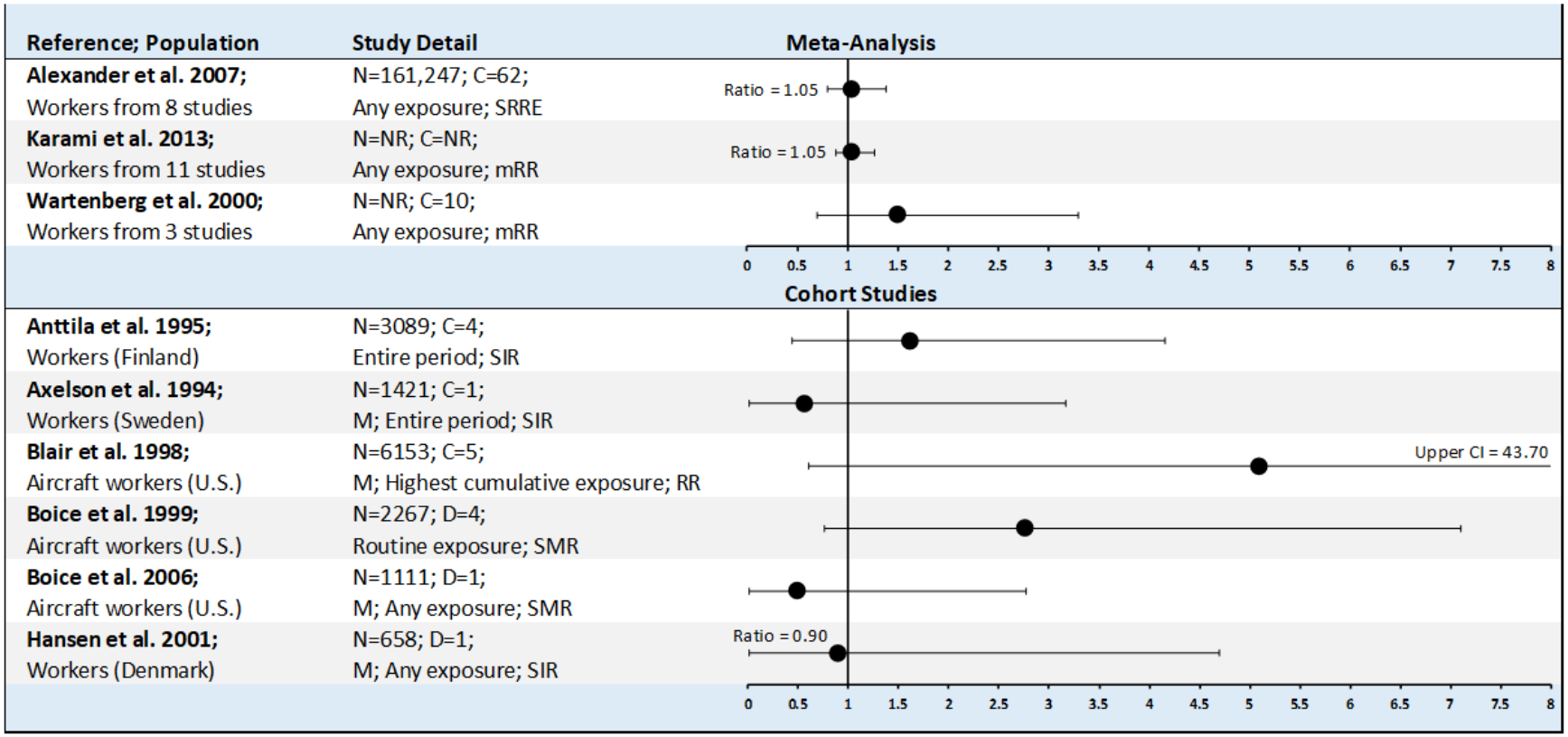
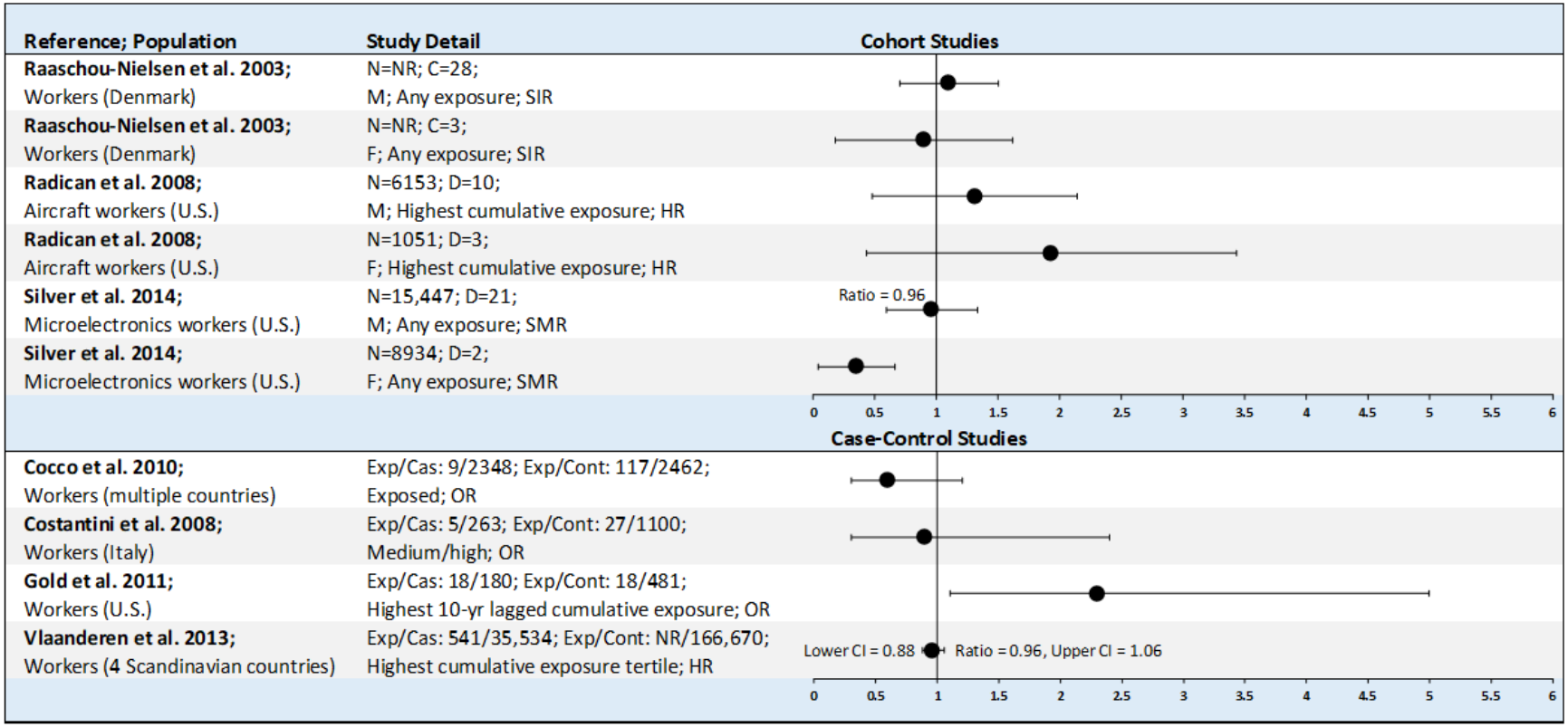


Figure 3-15 *(continued)*. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Multiple Myeloma



= risk estimate and 95% CI

C = number with multiple myeloma; CI = confidence interval; D = number of deaths due to multiple myeloma; Exp/Cas = number of exposed cases/number of cases; Exp/Cont = number of exposed controls/number of controls; F = females; HR = hazard ratio; M = males; mRR = relative risk ratio; N = number of participants; NR = not reported; OR = odds ratio; RR = rate ratio; SIR = standardized incidence ratio; SMR = standardized mortality ratio; SRRE = summary relative risk estimate; yr = year

Figure 3-16. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Leukemia

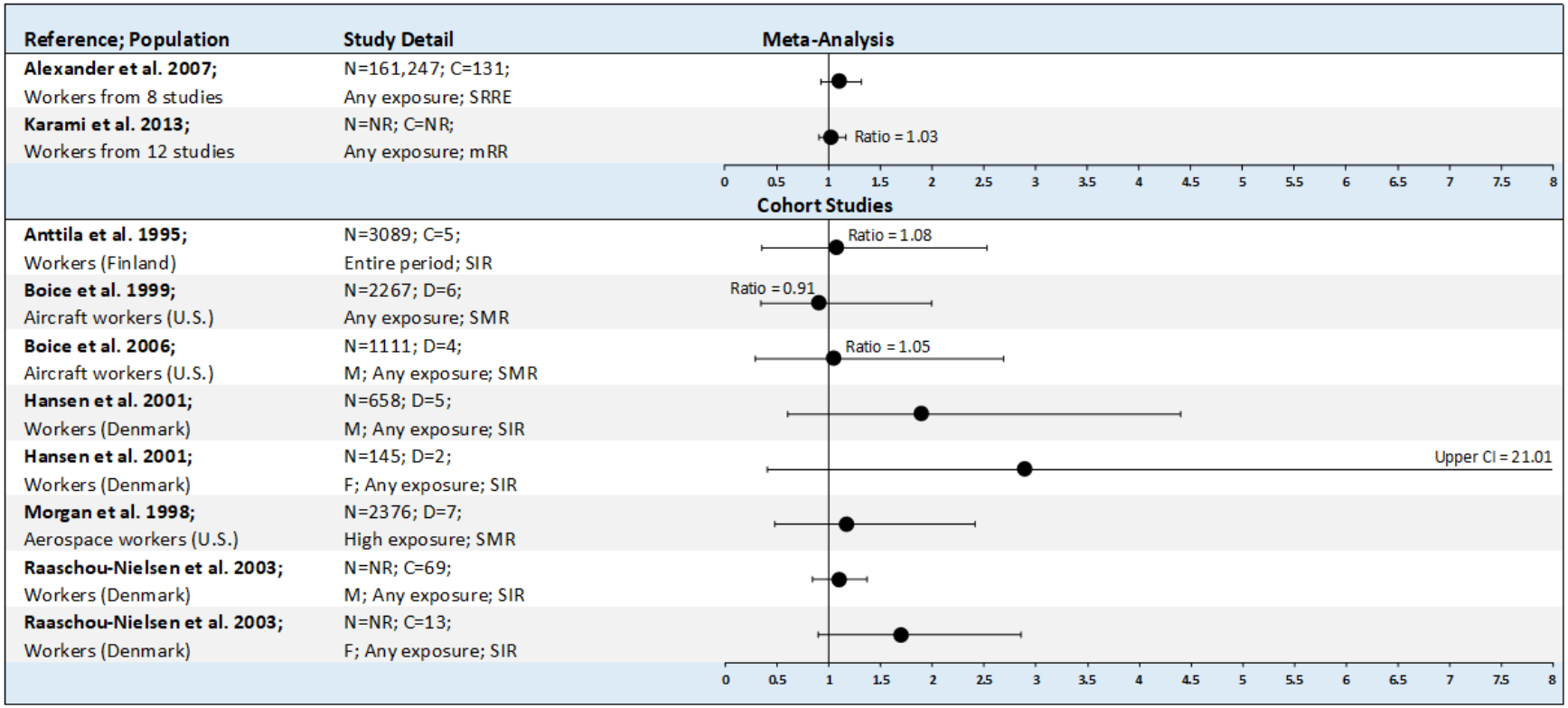
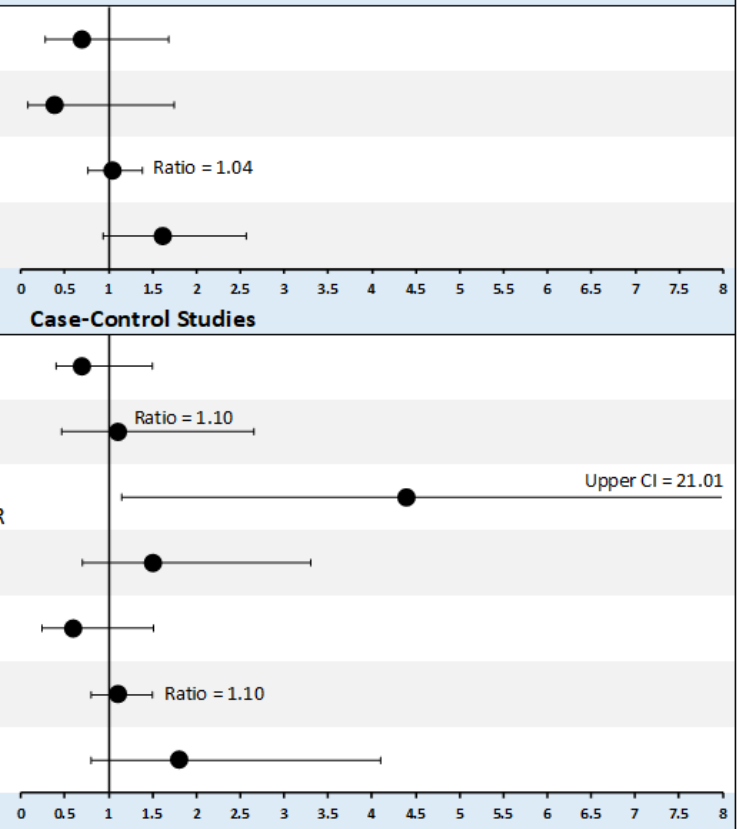


Figure 3-16 *(continued)*. Summary of Epidemiological Studies Evaluating Associations between Inhaled Trichloroethylene and Leukemia

Reference; Population	Study Detail
Cohort Studies	
Radican et al. 2008; Aircraft workers (U.S.)	N=6153; D=9; M; Highest cumulative exposure; HR
Radican et al. 2008; Aircraft workers (U.S.)	N=1051; D=2; F; Highest cumulative exposure; HR
Silver et al. 2014; Microelectronics workers (U.S.)	N=15,447; D=45; M; Any exposure; SMR
Silver et al. 2014; Microelectronics workers (U.S.)	N=8934; D=17; F; Any exposure; SMR
Case-Control Studies	
Costantini et al. 2008; Workers (Italy)	Exp/Cas: 11/586; Exp/Cont: 29/1278; Medium/high; OR
Greenland et al. 1994; Workers (U.S.)	Exp/Cas: NR/NR; Exp/Cont: NR/NR; Exposed; OR
McKinney et al. 1991; Children of workers (U.K.)	Exp/Cas: 7/109; Exp/Cont: 3/206; Exposure during periconception and gestation; OR
Nordstrom et al. 1998; Workers (Sweden)	Exp/Cas: 9/121; Exp/Cont: 26/484; M; Exposed; OR
Saberi Hosnijeh et al. 2013; Workers (Europe)	Exp/Cas: 5/109; Exp/Cont: 7865/137,084; High exposure; HR
Shu et al. 1999; Children of workers (U.S., CAN, and AUS)	Exp/Cas: 136/1018; Exp/Cont: 104/1076; Any paternal exposure; OR
Shu et al. 1999; Children of workers (U.S., CAN, and AUS)	Exp/Cas: 15/824; Exp/Cont: 9/910; Any maternal exposure; OR



—●— = risk estimate and 95% CI

AUS = Australia; C = number with leukemia; CAN = Canada; CI = confidence interval; D = number of deaths due to leukemia; Exp/Cas = number of exposed cases/number of cases; Exp/Cont = number of exposed controls/number of controls; F = females; HR = hazard ratio; M = males; mRR = relative risk ratio; N = number of participants; NR = not reported; OR = odds ratio; SMR = standardized mortality ratio; SRRE = summary relative risk estimate

Figures 3-2 through 3-16 include information on exposure type (e.g., specific industry or general occupational exposure), number of participants, cancer incidence, and study statistics (e.g., risk values and CIs) as reported by the study authors. For studies that evaluated males, females, and combined males and females, if risk values were similar, results for combined males and females are presented; however, if results differed between these groups, values for all groups are presented. For studies evaluating males and females separately (with no combined group), data for both are presented. Exposure classifications (e.g., qualitative exposure or classification of estimated cumulative exposure) for presented risk values also are included. If specific data were adjusted for exposure duration or latency period, this is noted.

Animal Studies. Statistically significant increases in the incidence of hepatomas (specific type of neoplasm not specified) occurred in male Swiss mice and in B6C3F1 mice of both sexes exposed to epoxide-free trichloroethylene (600 ppm) for 78 weeks. In contrast, a decrease in hepatomas was seen at 100 ppm in male Swiss mice; the statistical significance of this finding was not reported (Maltoni et al. 1986, 1988). In a retest with male B6C3F1 mice, a decrease in leukemias was seen (statistical significance not reported), with the percentage of hepatomas about the same for all dose levels and controls. There was also a significant increase in pulmonary tumors in male Swiss mice inhaling 600 ppm. Pulmonary tumors were also increased among treated female B6C3F1 mice but not among the males. Incidences were significantly increased over controls at 600 ppm for lung tumors in the female B6C3F1 mice and at 600 ppm for liver tumors in both sexes of B6C3F1 mice. Statistically significant, exposure concentration-related increased incidence of testicular Leydig cell tumors was reported in male Sprague-Dawley rats exposed to trichloroethylene at 0, 100, 300, or 600 ppm for 104 weeks (incidences of 5/95, 11/90, 24/90, and 22/90, respectively) (Maltoni et al. 1986, 1988).

The incidence of pulmonary adenocarcinomas was significantly increased over controls in female ICR mice exposed to 150 or 450 ppm reagent-grade trichloroethylene for 104 weeks, 5 days/week, 7 hours/day (Fukuda et al. 1983). There was no significant increase in other tumors in the mice or in similarly exposed female Sprague-Dawley rats. Henschler et al. (1980) reported statistically significant increases in the incidence and rate of development of malignant lymphomas in female NMRI mice (but not male NMRI mice or male or female Wistar rats or Syrian hamsters) exposed to trichloroethylene by inhalation at 100 or 500 ppm for 18 months. Incidences of malignant lymphomas in controls, 100 ppm, and 500 ppm groups were 9/29, 17/30, and 18/28, respectively. However, this type of tumor is historically common in unexposed female mice, possibly induced virally, and these investigators suggested that it may have resulted from immunosuppression.

The lowest concentrations resulting in cancer in reliable animal studies are indicated as CELs in Table 3-1 and Figure 3-1.

3.2.2 Oral Exposure

3.2.2.1 Death

Human studies have reported hepatorenal failure as the cause of death following accidental or intentional ingestion of trichloroethylene (De Baere et al. 1997; Kleinfeld and Tabershaw 1954; Liotier et al. 2008; Secchi et al. 1968; Vattemi et al. 2005). It was not possible to determine an accurate dose in these cases.

Acute oral LD_{50} values have been determined for mice (2,402 mg/kg) (Tucker et al. 1982) and rats (7,208 mg/kg) (Smyth et al. 1969). In a study in which pregnant rats were treated by gavage with trichloroethylene in corn oil on GDs 6–15, 2 of 13 died at 1,125 mg/kg/day, while all survived at 844 mg/kg/day (Narotsky et al. 1995). The lethality of trichloroethylene may be related to the delivery vehicle. Administration of trichloroethylene in an aqueous Emulphor vehicle proved to be more lethal but less hepatotoxic than similar administration of trichloroethylene in corn oil during a 4-week exposure period (Merrick et al. 1989). Further explanation of these study results is included in Section 3.2.2.2, under Hepatic Effects. Deaths of rats and mice have occurred following intermediate-duration exposure in range-finding studies and during chronic-duration cancer studies (Henschler et al. 1984; NCI 1976; NTP 1990). The premature deaths were the result of tumors or other conditions (body weight loss, respiratory infection, renal failure, and central nervous system depression) caused by very high daily doses. Further explanation of these studies is included in Section 3.2.2.7. LD_{50} values and the lowest doses causing death in rats and mice are recorded in Table 3-3 and plotted in Figure 3-17.

3.2.2.2 Systemic Effects

The highest NOAEL and all reliable LOAELs for each species, duration, and end point for systemic effects following oral exposure are recorded in Table 3-3 and plotted in Figure 3-17.

Respiratory Effects. Pulmonary congestion and edema were observed in a 43-year-old male who died following an oral overdose of trichloroethylene (De Baere et al. 1997). One study suggested increased respiratory disorders (asthma, bronchitis, pneumonia) in children with chronic exposure to a solvent-contaminated water supply (Byers et al. 1988). Two municipal wells in eastern Woburn, Massachusetts, were found to contain several solvents including trichloroethylene (267 ppb) and

Table 3-3. Levels of Significant Exposure to Trichloroethylene - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (Sprague-Dawley)	Gd 6-15 (GO)				1125 F (2/13 died)	Narotsky et al. 1995	
2	Rat (Fischer- 344)	2 wk ad libitum (F)		6618			NTP 1986	
3	Rat (NS)	once (G)				7208 (LD50)	Smyth et al. 1969	
4	Mouse (CD-1)	14 d ad libitum (F)		12180			NTP 1985	
5	Mouse (CD-1)	once (G)				2402 M (LD50) 2443 F (LD50)	Tucker et al. 1982	
Systemic								
6	Rat (Fischer- 344)	14 d (GO)	Hepatic	500 F	1500 F (increased liver weight, hepatocellular hypertrophy)		Berman et al. 1995	
			Renal		50 F (increased kidney weight)			
			Endocr	1500 F				

Table 3-3. Levels of Significant Exposure to Trichloroethylene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
7	Rat (Wistar)	10 d 1 x/d (GO)	Hepatic	2000 M			Elcombe 1985	
8	Rat (Fischer- 344)	10 d 1 x/d (GO)	Hepatic		1000 M (22% increased liver weight, 1.8-fold greater palmitoyl CoA oxidation activity)		Goldsworthy and Popp 1987	
			Renal	1000 M				
			Bd Wt	1000 M				
9	Rat (Fischer- 344)	10 d 1 x/d (GO)	Renal	1000			Goldsworthy et al. 1988	
10	Rat (Fischer- 344)	Gd 6-19 (GO)	Resp	1125 F		1500 F (rales, dyspnea)	Narotsky and Kavlock 1995	
			Bd Wt			1125 F (maternal body weight gain 45% lower than controls)		
11	Rat (Sprague-Dawley)	Gd 6-15 (GO)	Bd Wt			475 F (31% decreased body weight gain)	Narotsky et al. 1995	

Table 3-3. Levels of Significant Exposure to Trichloroethylene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
12	Rat (Fischer- 344)	2 wk ad libitum (F)	Bd Wt	584	1358 (16% decreased body weight gain)		NTP 1986	
13	Rat (Sprague-Dawley)	7 d 1x/d (GO)	Hepatic		2000 M (12-16% increased absolute and relative liver weight)		Nunes et al. 2001	
			Bd Wt	2000 M				
14	Rat (Osborne-Mendel)	3 d 1 x/d (GO)	Hepatic	1100 M			Stott et al. 1982	
			Renal	1100 M				
15	Mouse (Swiss-Webster)	10 d 1 x/d (GO)	Hepatic	50 M	100 M (2-fold increase in palmitoyl CoA oxidation)		Elcombe 1985	
16	Mouse (B6C3F1)	10 d 1 x/d (GO)	Hepatic		1000 M (50% increased liver weight, 6.25-fold greater palmitoyl CoA oxidation activity)		Goldsworthy and Popp 1987	
			Renal	1000 M				
			Bd Wt	1000 M				

Table 3-3. Levels of Significant Exposure to Trichloroethylene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
17	Mouse (CD-1)	14 d ad libitum (F)	Hepatic	1000	2479 (increased liver weight)		NTP 1985	
			Bd Wt	12180				
18	Mouse (B6C3F1)	3 d 1 x/d (GO)	Hepatic		2400 M (hepatic hypertrophy, centrilobular swelling)		Stott et al. 1982	
			Renal	2400 M				
19	Mouse (CD-1)	14 d 1 x/d (G)	Hemato	240 M			Tucker et al. 1982	
			Hepatic	240 M				
			Renal	240 M				
			Bd Wt	240 M				
Neurological								
20	Rat (Fischer- 344)	14 d (GO)		150 F	500 F (increased rearing)		Moser et al. 1995	
21	Rat (Sprague-Dawley)	Gd 6-15 (GO)		475 F		633 F (transient ataxia)	Narotsky et al. 1995	
22	Rat (Sprague-Dawley)	7 d 1x/d (GO)			2000 M (25% increased foot splay)		Nunes et al. 2001	

Table 3-3. Levels of Significant Exposure to Trichloroethylene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Reproductive								
23	Rat (Sprague-Dawley)	14 d (W)			143 M (decreased in vitro fertilization capacity of sperm)		DuTeaux et al. 2004	
Developmental								
24	Rat (Sprague-Dawley)	Gd 6-15 (GO)		844		1125 (increased prenatal loss, micro- or anophthalmia)	Narotsky et al. 1995	
25	Mouse (B6D2F1)	Gd 1-5 Gd 6-10 Gd 1-15 1 x/d (GO)		240			Cosby and Dukelow 1992	
26	Mouse (NMRI)	7 d 1 x/d (GO)			50 M (reduced rearing rate at 60 days of age)		Fredriksson et al. 1993	
INTERMEDIATE EXPOSURE								
Death								
27	Rat (Long- Evans)	2 wk 5 d/wk Gd 0-21 7 d/wk (GO)				1000 (4/23 died)	Manson et al. 1984	
28	Rat (Osborne-Mendel)	6 wk 5 d/wk 1 x/d (GO)				5620 (10/10 died)	NCI 1976	

Table 3-3. Levels of Significant Exposure to Trichloroethylene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
29	Mouse (B6C3F1)	4 wk 5 d/wk 1 x/d (GW)				1200 M (2/12 deaths) 900 F (2/12 deaths)	Merrick et al. 1989	
30	Mouse (B6C3F1)	6 wk 5 d/wk 1 x/d (GO)				5620 M (4/5 deaths) 3160 F (2/5 deaths)	NCI 1976	
31	Mouse (B6C3F1)	13 wk 5 d/wk 1 x/d (GO)				1500 M (2/10 died) 3000 F (1/10 died)	NTP 1990	
Systemic								
32	Rat (Long- Evans)	2 wk 5 d/wk Gd 0-21 7 d/wk (GO)	Bd Wt			1000 (34% depressed body weight gain)	Manson et al. 1984	
33	Rat (Fischer- 344)	18 wk ad libitum (F)	Hepatic	316	632 (19-24% increased relative liver weight in F0 rats)		NTP 1986	
			Bd Wt		158 F (10% lower terminal body weight)			

Table 3-3. Levels of Significant Exposure to Trichloroethylene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
34	Rat (Fischer- 344)	13 wk 5 d/wk 1 x/d (GO)	Resp		1000 F (pulmonary vasculitis involving small veins in 6/10)		NTP 1990	
			Cardio	2000 M				
			Gastro	2000 M				
			Musc/skel	2000 M				
			Hepatic	2000 M				
			Renal		1000 F (minimal or mild cytomegaly, karyomegaly of renal tubular epithelial cells in 5/10)			
			Endocr	2000 M				
			Dermal	2000 M				
			Bd Wt	1000 M		2000 M (body weights 24% less than controls)		
35	Rat (Osborne-Mendel)	3 wk 5 d/wk 1 x/d (GO)	Hepatic	1100 M			Stott et al. 1982	
			Renal	1100 M				
			Bd Wt	1100 M				
36	Rat (Wistar)	16 wk (W)	Bd Wt	206 M			Waseem et al. 2001	

Table 3-3. Levels of Significant Exposure to Trichloroethylene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
37	Mouse (Hybrid)	10-11 wk (W)	Bd Wt			122 (30% depressed terminal body weight)	Blossom and Doss 2007	
38	Mouse (Hybrid)	Up to 63 d (W)	Bd Wt	31			Blossom et al. 2008	
39	Mouse (Swiss- Cox)	6 wk 5 d/wk 1 x/d (GO)	Hepatic	100 M	400 M (enlarged hepatocytes)	1600 M (central lobular necrosis)	Buben and O'Flaherty 1985	
			Bd Wt	3200				
40	Mouse (Hybrid)	36 or 48 wk (W)	Bd Wt		60 F (26% decreased body weight gain after 11 weeks of treatment)		Cai et al. 2008	
41	Mouse (Hybrid)	Up to 22 wk (W)	Hepatic	734 F			Griffin et al. 2000a; Gilbert et al. 1999	
			Renal	734 F				
			Bd Wt	734 F				
42	Mouse (Hybrid)	4 or 32 wk (W)	Bd Wt	400 F			Griffin et al. 2000b	

Table 3-3. Levels of Significant Exposure to Trichloroethylene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
43	Mouse (B6C3F1)	30 wk (W)	Hepatic	3.5 F			Keil et al. 2009	
			Renal	3.5 F				
			Bd Wt	3.5 F				
44	Mouse (Hybrid)	30 wk (W)	Hepatic	2.2 F			Keil et al. 2009	
			Renal	2.2 F				
			Bd Wt	2.2 F				
45	Mouse (B6C3F1)	4 wk 5 d/wk 1 x/d (G)	Hepatic		450 F (117% increase in relative liver weight)	600 M (focal necrosis, 136% increase in relative liver weights)	Merrick et al. 1989	
			Bd Wt	2400 M				
46	Mouse (CD-1)	18 wk ad libitum (F)	Hepatic		737 (increased liver weight, hepatocellular hypertrophy)		NTP 1985	
			Renal		737 (tubular degeneration and karyomegaly of the corticomedullary renal tubular epithelium in F0 males and females)			
			Bd Wt	737				

Table 3-3. Levels of Significant Exposure to Trichloroethylene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
47	Mouse (B6C3F1)	3 wk 5 d/wk 1 x/d (GO)	Hepatic	250 M	500 M (liver enlargement, increased DNA content per gram tissue)	1200 M (liver enlargement, increased DNA content, centrilobular hepatocyte swelling)	Stott et al. 1982	
			Renal	2400 M				
			Bd Wt	2400 M				
48	Mouse (CD-1)	6 mo ad libitum (W)	Gastro	18 M 793 F	217 M (gas pockets in the intestinal coating, blood in the intestines in 5)		Tucker et al. 1982	
			Hemato	393 M 793 F	660 M (red blood cell counts 16% lower than controls)			
			Hepatic	793 F				
			Renal	217 M 437 F	393 M (elevated urinary protein and ketones)			
					793 F (elevated urinary protein and ketones)			
			Bd Wt	393 M	660 M (body weights 11% lower than controls, associated with decreased water intake)			

Table 3-3. Levels of Significant Exposure to Trichloroethylene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Immuno/ Lymphoret								
49	Mouse (Hybrid)	10-11 wk (W)			122 (decreased splenic T- and B-lymphocytes)		Blossom and Doss 2007	
50	Mouse (Hybrid)	Up to 63 d (W)			31 (altered immunoregulation)		Blossom et al. 2008	
51	Mouse (Hybrid)	36 or 48 wk (W)			60 F (inflammation in liver, kidney, lungs, and pancreas)		Cai et al. 2008	
52	Mouse (Hybrid)	Up to 22 wk (W)			455 F (increased serum antinuclear antibodies and total serum immunoglobulins at 4 and 8 weeks indicative of accelerated autoimmune response)		Griffin et al. 2000a; Gilbert et al. 1999	
53	Mouse (Hybrid)	4 or 32 wk (W)			21 F (multiple indicators of autoimmune hepatitis)		Griffin et al. 2000b	
54	Mouse (B6C3F1)	30 wk (W)			0.35[b] F (30% decreased thymus weight, increased serum levels of IgG and selected autoantibodies)		Keil et al. 2009	

Table 3-3. Levels of Significant Exposure to Trichloroethylene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
55	Mouse (Hybrid)	30 wk (W)		2.2 F			Keil et al. 2009	
56	Mouse (B6C3F1)	Gd 0-21 and 3 or 8 wk PPD (W)			0.37[b] (decreased PFC response in male and female pups, increased hypersensitivity response in male pups)		Peden-Adams et al. 2006	
57	Mouse (CD-1)	4 or 6 mo ad libitum (W)			18 F (suppressed cell-mediated immune response, inhibited bone marrow stem cell colonization)		Sanders et al. 1982	Dose estimates from earlier study report (Tucker et al. 1982)
58	Mouse	48 wk (W)			1051 F (accelerated autoimune response in autoimmune-prone MRL+/+ mice)		Wang et al. 2007b	
Neurological								
59	Rat (Sprague-Dawley)	10 wk 5 d/wk 1 x/d (GO)			2500 F (altered myelin thickness of the trigeminal nerve)		Barret et al. 1991	

Table 3-3. Levels of Significant Exposure to Trichloroethylene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
60	Rat (Sprague-Dawley)	10 wk 5 d/wk 1 x/d (GO)			2500 F (altered trigeminal nerve morphometrics, fatty acid composition indicative of demyelination)		Barret et al. 1992	
61	Rat (Fischer- 344)	6 wk 5 d/wk 1 x/d (GO)				1000 M (decreased dopaminergic neurons in substantia nigra)	Gash et al. 2008	
62	Rat (Wistar)	16 wk (W)		206 M			Waseem et al. 2001	
Reproductive								
63	Rat (Fischer- 344)	18 wk ad libitum (F)		158			NTP 1986	
					316 (9% decrease in number of liveborn pups)			
64	Rat (Long- Evans)	6 wk 5 d/wk 1 x/d (GO)		100 M		1000 M (impaired copulatory behavior, mount/ ejaculation latency, intromissions)	Zenick et al. 1984	
65	Mouse (CD-1)	17 wk ad libitum (F)		375 M 750 F	750 M (18-45% decreased sperm motility)		NTP 1985	

Table 3-3. Levels of Significant Exposure to Trichloroethylene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
66	Mouse (CD-1)	18 wk ad libitum (F)		362 M	737 M (decreased sperm motility in F0 and F1 males)		NTP 1985	
Developmental								
67	Rat (Sprague-Dawley)	2-3 mo before mating and/or gestation ad libitum (W)				0.218 (increased fetal heart abnormalities)	Dawson et al. 1993; Johnson et al. 1998	
68	Rat (Sprague-Dawley)	14 d before mating Gd 0-21 -weaning ad libitum (W)				37 M (40% decrease in number of myelinated fibers in the hippocampus)	Isaacson and Taylor 1989	
69	Rat (Sprague-Dawley)	Throughout gestation (22 d) (W)		0.00045		0.048[b] (increased incidence of congenital heart abnormalities)	Johnson et al. 2003	
70	Rat (Long- Evans)	2 wk 5 d/wk Gd 0-21 7 d/wk (GO)		100		1000 (decreased neonatal survival)	Manson et al. 1984	Serious maternal toxicity at 1000 mg/kg/day (4/23 died, 34% depressed body weight gain)

Table 3-3. Levels of Significant Exposure to Trichloroethylene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
71	Rat (Fischer- 344)	18 wk ad libitum (F)			158 (11-13% decreased pup body weight at PND 21		NTP 1986	
72	Rat (Sprague-Dawley)	14 d before mating Gd 0-21 -weaning ad libitum (W)			37 M (increased exploratory behavior)		Taylor et al. 1985	
73	Mouse (MRL +/+)	GD0-birth (W)			2.96 F (Increased locomotor activity in male pups tested on PND 42)		Blossom et al. 2017	
74	Mouse (CD-1)	17 wk ad libitum (F)		375 M		750 (increased perinatal mortality)	NTP 1985	
75	Mouse (CD-1)	18 wk ad libitum (F)		362		737 (increased perinatal mortality)	NTP 1985	
76	Mouse (B6C3F1)	Gd 0-21 and 3 or 8 wk PPD (W)			0.37 (18% decreased body weight in 3-week-old pups)		Peden-Adams et al. 2006	

Table 3-3. Levels of Significant Exposure to Trichloroethylene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
CHRONIC EXPOSURE								
Death								
77	Rat (Osborne-Mendel)	78 wk 5 d/wk 1 x/d (GO)				1097 M (47/50 died) 549 F (35/48 died)	NCI 1976	
78	Rat (Fischer- 344)	103 wk 5 d/wk 1 x/d (GO)				500 M (30/50 died) 500 F (17/50 died)	NTP 1990	
79	Mouse (B6C3F1)	78 wk 5 d/wk 1 x/d (GO)				869 F (8/50 died)	NCI 1976	
80	Mouse (B6C3F1)	103 wk 5 d/wk 1 x/d (GO)				1000 M (34/50 died)	NTP 1990	

Table 3-3. Levels of Significant Exposure to Trichloroethylene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Systemic								
81	Rat (Sprague-Dawley)	52 wk 5 d/wk 1 x/d (GO)	Resp	250			Maltoni et al. 1986	
			Cardio	250				
			Gastro	250				
			Musc/skel	250				
			Hepatic	250				
			Renal	50 M	250 M			
			Endocr	250				
			Dermal	250				
			Ocular	250				
			Bd Wt	250				

Table 3-3. Levels of Significant Exposure to Trichloroethylene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
82	Rat (Osborne-Mendel)	78 wk 5 d/wk 1 x/d (GO)	Resp	1097			NCI 1976	
			Cardio	1097				
			Gastro	1097				
			Musc/skel	1097				
			Hepatic	1097				
			Renal		549 (toxic nephrosis, proximal tubular epithelium alterations)			
			Endocr	1097				
			Dermal		549 (alopecia, roughening of hair coat, sores)			
			Ocular		549 (squinting, red discharge)			
			Bd Wt	549 M	1097 M (body weights 18% lower than controls at 78 weeks)			
					549 F (body weights 15% lower than controls at 78 weeks)			

Table 3-3. Levels of Significant Exposure to Trichloroethylene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
83	Rat (August)	103 wk 5 d/wk 1 x/d (GO)	Resp	1000			NTP 1988	
			Cardio	1000				
			Gastro	1000				
			Musc/skel	1000				
			Hepatic	1000				
			Renal		500 (toxic nephrosis 20% of males and 17% of females, cytomegaly)			
			Endocr	1000				
			Dermal	1000				
			Ocular	1000				
			Bd Wt	500 M	1000 M (body weights 12.3% lower than controls)			

Table 3-3. Levels of Significant Exposure to Trichloroethylene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
84	Rat (Marshall)	103 wk 5 d/wk 1 x/d (GO)	Resp	1000			NTP 1988	
			Cardio	1000				
			Gastro	1000				
			Musc/skel	1000				
			Hepatic	1000				
			Renal		500 (toxic nephrosis 36% of males and 63% of females, cytomegaly)			
			Endocr	1000				
			Dermal	1000				
			Ocular	1000				
			Bd Wt	500 F	1000 F (body weights 10.1% lower than controls)			

Table 3-3. Levels of Significant Exposure to Trichloroethylene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
85	Rat (ACI)	103 wk 5 d/wk 1 x/d (GO)	Resp	1000			NTP 1988	
			Cardio	1000				
			Gastro	1000				
			Musc/skel	1000				
			Hepatic	1000				
			Renal		500 (toxic nephrosis 37% of males and 45% of females, cytomegaly)			
			Endocr	1000				
			Dermal	1000				
			Ocular	1000				
			Bd Wt		500 M (body weights 11% lower than controls)			

Table 3-3. Levels of Significant Exposure to Trichloroethylene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
86	Rat (Osborne-Mendel)	103 wk 5 d/wk 1 x/d (GO)	Resp	1000			NTP 1988	
			Cardio	1000				
			Gastro	1000				
			Musc/skel	1000				
			Hepatic	1000				
			Renal		500 (toxic nephrosis 78% of males and 60% of females, cytomegaly)			
			Endocr	1000				
			Dermal	1000				
			Ocular	1000				
			Bd Wt	500 M	1000 M (body weights 11.6% lower than controls)			

Table 3-3. Levels of Significant Exposure to Trichloroethylene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
87	Rat (Fischer- 344)	103 wk 5 d/wk 1 x/d (GO)	Resp	1000			NTP 1990	
			Cardio	1000				
			Gastro	1000				
			Hepatic	1000				
			Renal		500 (slight to well marked toxic nephrosis, cytomegaly)			
			Endocr	1000				
			Dermal	1000				
			Bd Wt	500 M	1000 M (body weights 13% lower than controls)			
					500 F (body weights 12% lower than controls)			

Table 3-3. Levels of Significant Exposure to Trichloroethylene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
88	Mouse (B6C3F1)	78 wk 5 d/wk 1 x/d (GO)	Resp	2239 M			NCI 1976	
			Cardio	2239 M				
			Gastro	2339 M				
			Musc/skel	2239 M				
			Hepatic	2239 M				
			Renal		1160 M (toxic nephrosis)			
					869 F (toxic nephrosis)			
			Endocr	2239 M				
			Dermal		869 F (alopecia, skin sores)			
			Ocular	2239 M				
			Bd Wt	2239 M				

Table 3-3. Levels of Significant Exposure to Trichloroethylene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
89	Mouse (B6C3F1)	103 wk 5 d/wk 1 x/d (GO)	Resp	1000			NTP 1990	
			Cardio	1000				
			Gastro	1000				
			Hepatic	1000				
			Renal		1000 (slight to moderate toxic nephrosis, cytomegaly)			
			Endocr	1000				
			Dermal	1000				
			Bd Wt		1000 M (body weights 10% lower than controls)			
90	Mouse (Hybrid)	Gd 0 through 12 mo (W)	Bd Wt	0.33 M 3.4 F	3.3 M (12% depressed mean terminal body weight)		Peden-Adams et al. 2008	Estimated doses based on direct exposure of the offspring via their drinking water; they had also been exposed during gestation and lactation

Table 3-3. Levels of Significant Exposure to Trichloroethylene - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Immuno/ Lymphoret								
91	Mouse (Hybrid)	Gd 0 through 12 mo (W)			0.33 M (29% decreased thymic cellularity)		Peden-Adams et al. 2008	Estimated doses based on direct exposure of the offspring via their drinking water; they had also been exposed during gestation and lactation
Cancer								
92	Rat (Fischer- 344)	103 wk 5 d/wk 1 x/d (GO)				1000 M (CEL: renal tubular cell adenocarcinomas)	NTP 1990	
93	Mouse (B6C3F1)	103 wk 5 d/wk 1 x/d (GO)				1000 (CEL: hepatocellular carcinomas)	NTP 1990	

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

b Study results used as support for the EPA (2011e) preferred chronic RfD of 0.0005 mg/kg/day for trichloroethylene and the ATSDR chronic-duration and intermediate-duration oral MRLs for trichloroethylene. The preferred chronic RfD of EPA is based on results of three critical studies for which individual candidate chronic RfDs were derived: A candidate chronic RfD of 0.00048 mg/kg/day for decreased thymus weight in female mice exposed to trichloroethylene in the drinking water for 30 weeks (Keil et al. 2009), a candidate chronic RfD of 0.00037 mg/kg/day for decreased plaque forming cell (PFC) response in 3- and 8-week-old pups and increased delayed-type hypersensitivity in 8-week-old pups exposed to trichloroethylene via the maternal drinking water throughout gestation and postnatally (until 3 or 8 weeks of age) via the drinking water (Peden-Adams et al. 2006), and a candidate chronic RfD of 0.00051 mg/kg/day for fetal heart malformations in rats exposed to trichloroethylene via the maternal drinking water during gestation (Johnson et al. 2003). Selected details regarding EPA's methodology for derivation of the preferred chronic RfD using results from the three critical studies are presented in Appendix A.

Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; (F) = feed; F = Female; (G) = gavage; Gastro = gastrointestinal; Gd = gestation day; (GO) = gavage in oil; (GW) = gavage in water; Hemato = hematological; IgG = Immunoglobulin G; Immuno/Lymphoret = immunological/lymphoreticular; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; PFC = plaque-forming cell; PND = post-natal day; PPD = post-parturition day; Resp = respiratory; (W) = drinking water; wk = week(s); x = time(s)

Figure 3-17. Levels of Significant Exposure to Trichloroethylene - Oral

Acute (≤14 days)

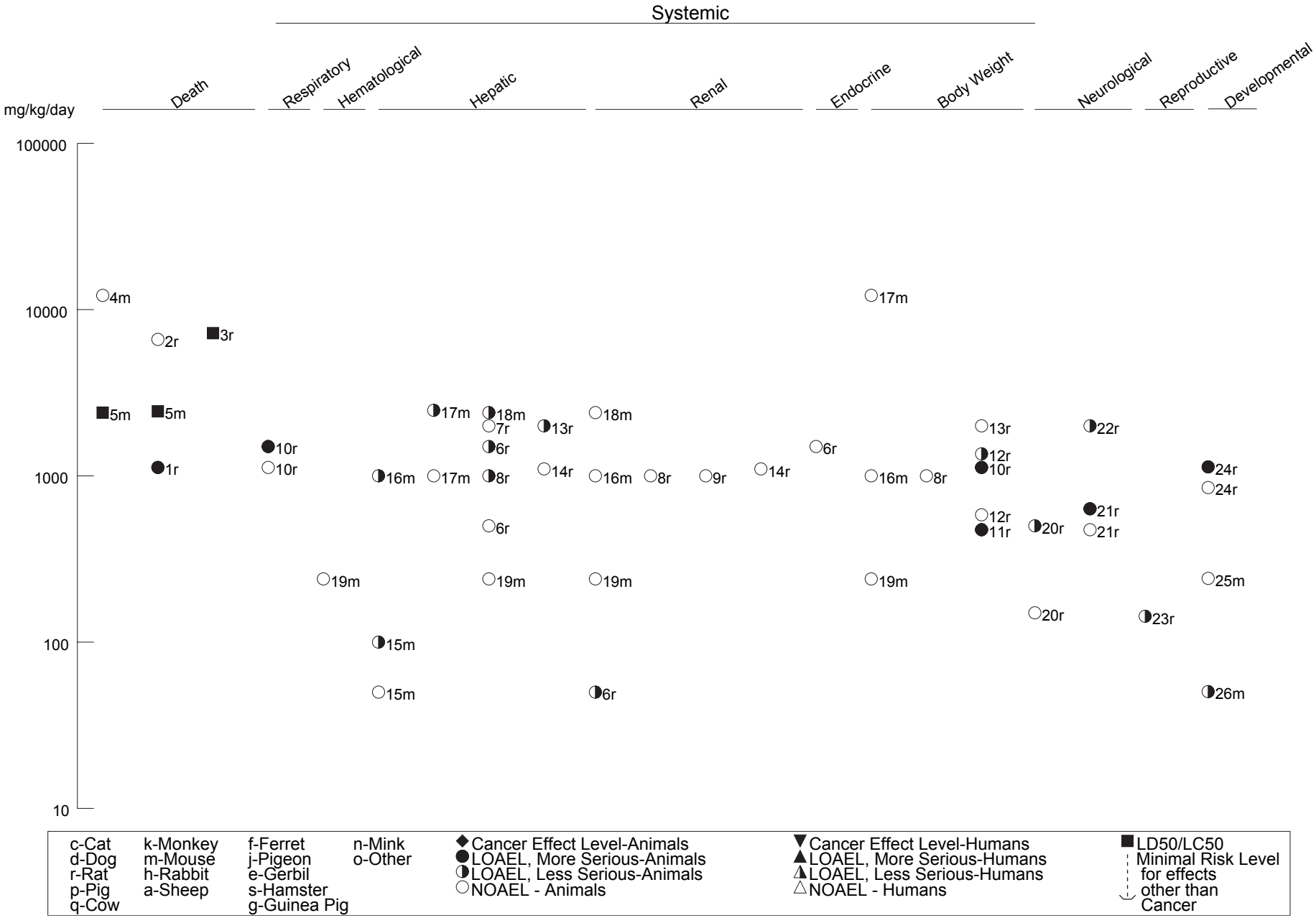


Figure 3-17. Levels of Significant Exposure to Trichloroethylene - Oral *(Continued)*

Intermediate (15-364 days)

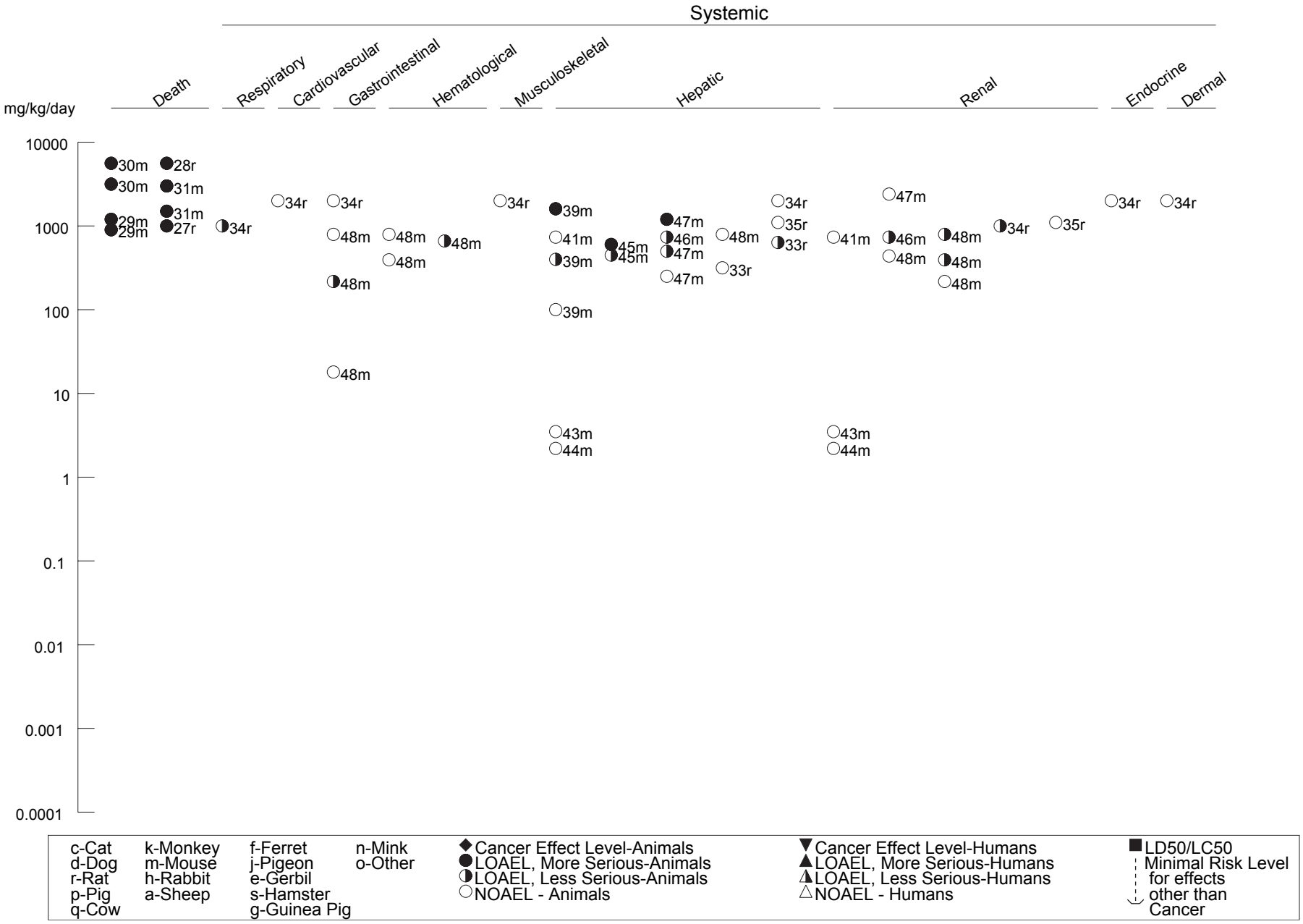


Figure 3-17. Levels of Significant Exposure to Trichloroethylene - Oral *(Continued)*

Intermediate (15-364 days)

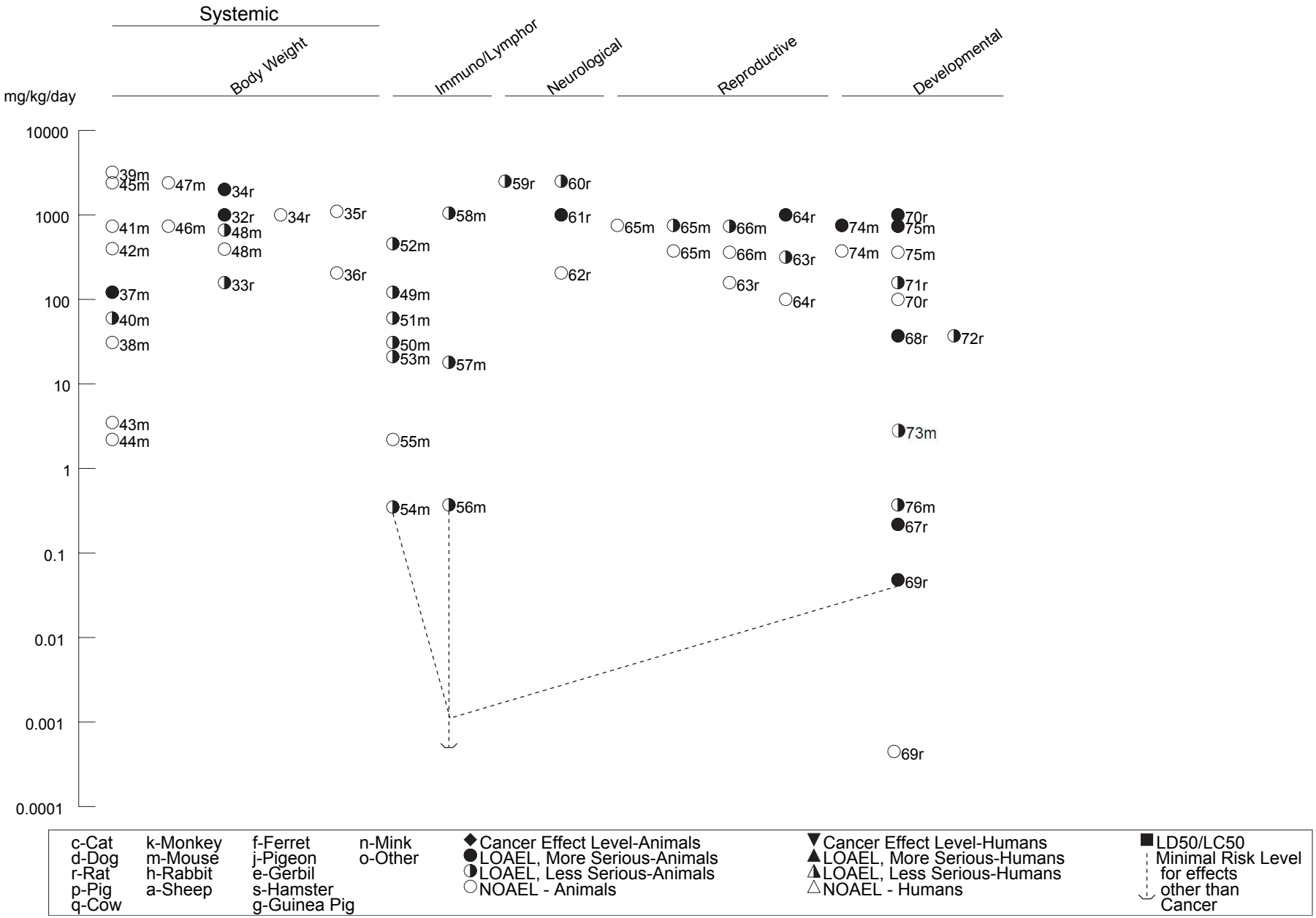


Figure 3-17. Levels of Significant Exposure to Trichloroethylene - Oral *(Continued)*

Chronic (≥365 days)

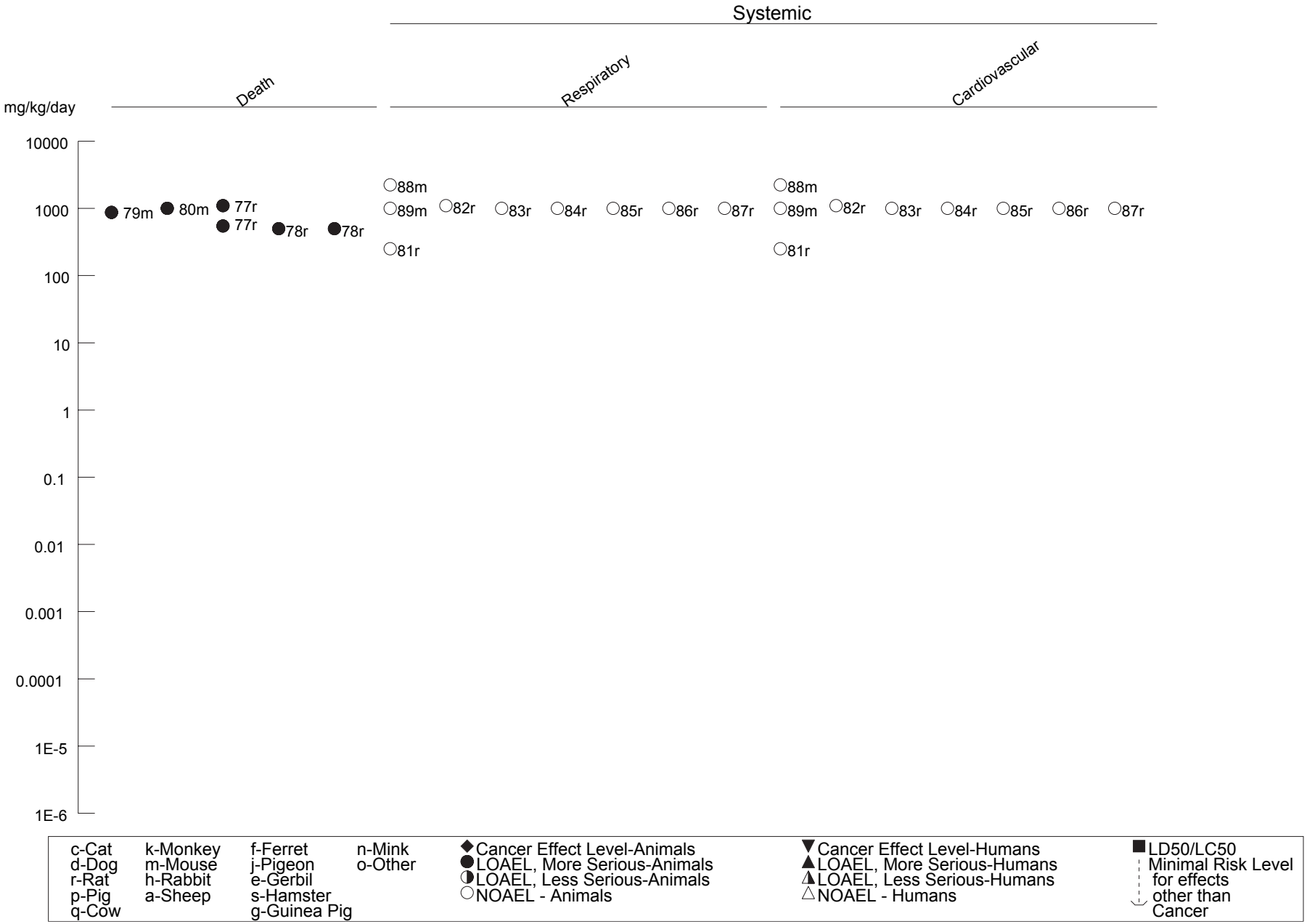


Figure 3-17. Levels of Significant Exposure to Trichloroethylene - Oral *(Continued)*

Chronic (≥365 days)

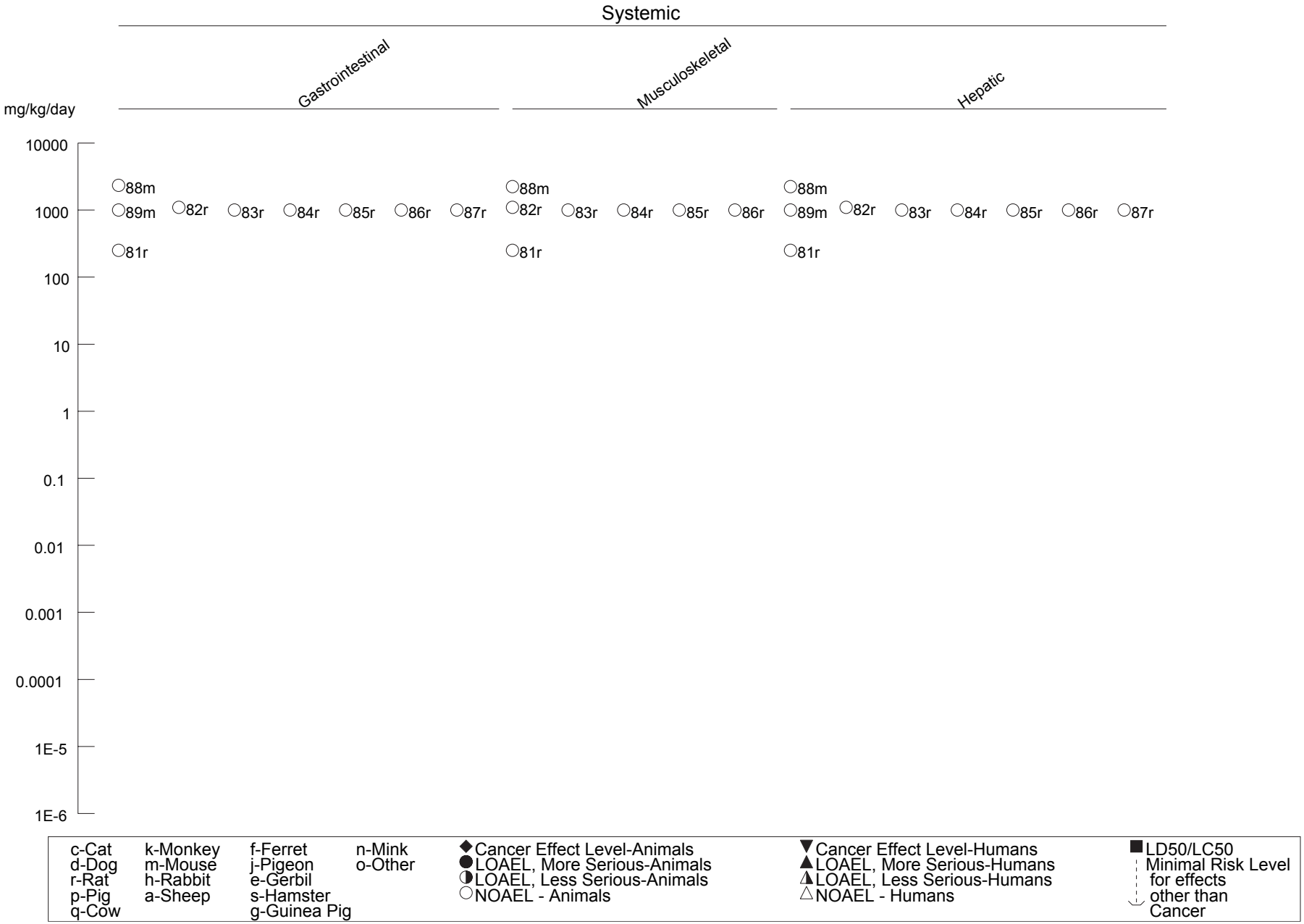


Figure 3-17. Levels of Significant Exposure to Trichloroethylene - Oral *(Continued)*

Chronic (≥365 days)

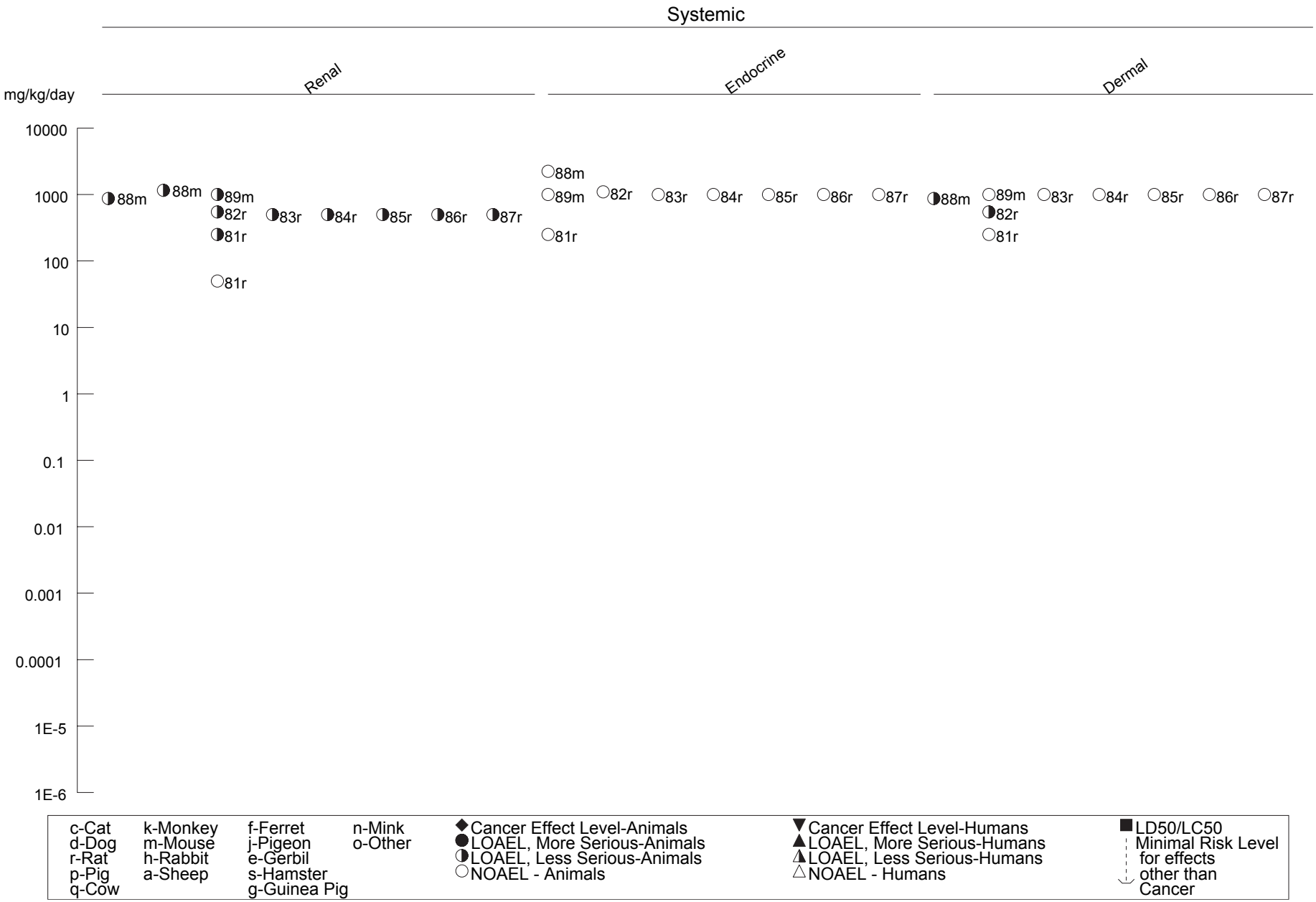
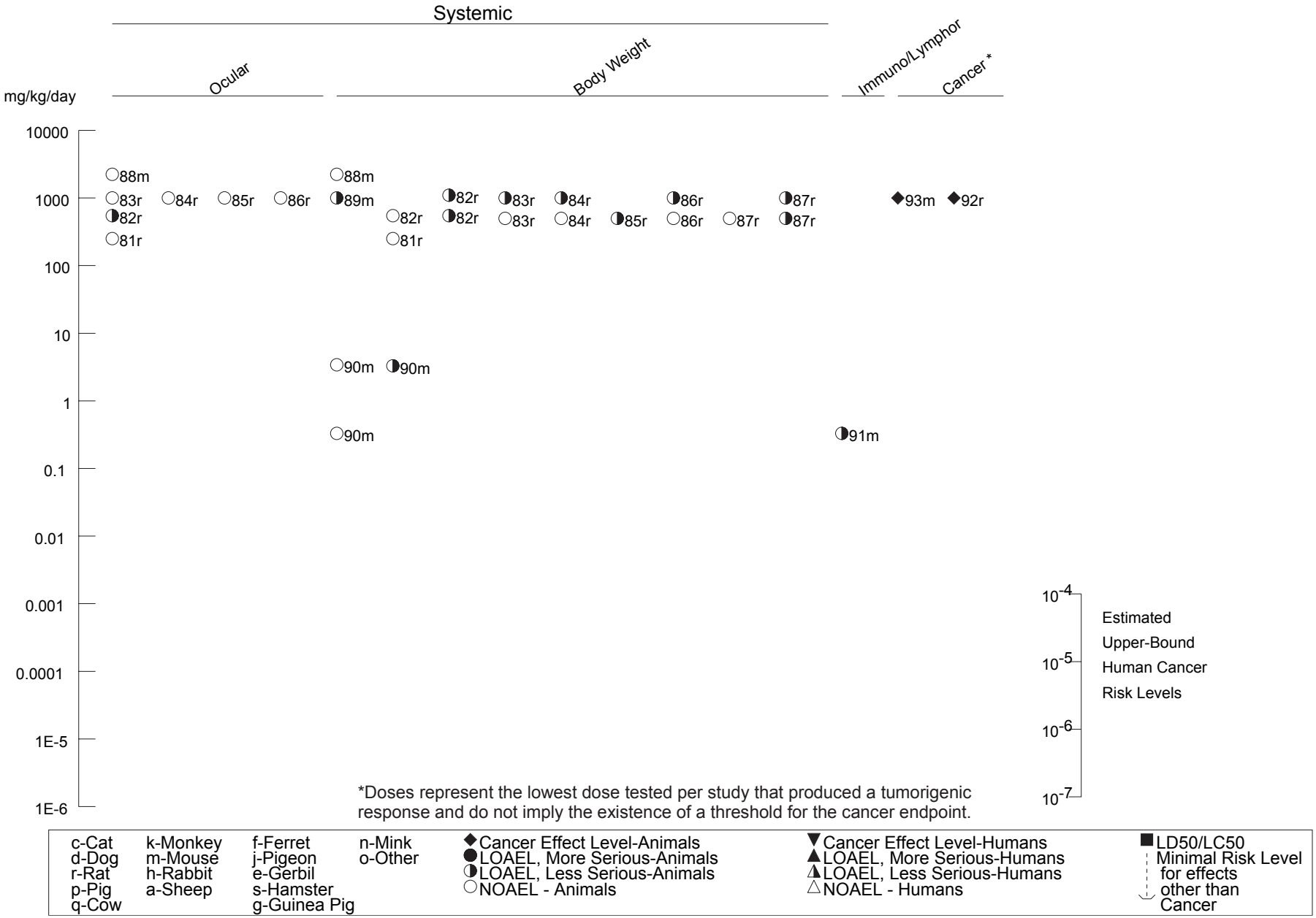


Figure 3-17. Levels of Significant Exposure to Trichloroethylene - Oral *(Continued)*

Chronic (≥365 days)



*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer endpoint.

c-Cat	k-Monkey	f-Ferret	n-Mink	◆Cancer Effect Level-Animals	▼Cancer Effect Level-Humans	■LD50/LC50
d-Dog	m-Mouse	j-Pigeon	o-Other	●LOAEL, More Serious-Animals	▲LOAEL, More Serious-Humans	Minimal Risk Level for effects other than Cancer
r-Rat	h-Rabbit	e-Gerbil		◑LOAEL, Less Serious-Animals	◭LOAEL, Less Serious-Humans	
p-Pig	a-Sheep	s-Hamster		○NOAEL - Animals	△NOAEL - Humans	
q-Cow		g-Guinea Pig				

tetrachloroethylene (21 ppb). The increased susceptibility to infection may be secondary to effects on the immune system. Accurate chemical-specific exposure levels for individuals could not be determined because the water distribution system was designed to use water from different wells at different rates and times. Other limitations of this study are described in Section 3.2.2.7.

Rales and dyspnea were observed in pregnant rats treated by gavage with 1,500 mg/kg/day trichloroethylene in corn oil on GDs 6–19 (Narotsky and Kavlock 1995). Respiratory effects were not observed at 1,125 mg/kg/day. Pulmonary vasculitis was observed in 6 of 10 female rats treated with 1,000 mg/kg/day (by gavage) and 6 of 10 male rats treated with 2,000 mg/kg/day (in corn oil) for 13 weeks (NTP 1990). This effect was also observed in 1 of 10 male and 1 of 10 female control rats. Histopathological examinations were not completed at the other doses in this study. Therefore, it is not possible to determine if this is a dose-related effect. Nonneoplastic histopathological changes in the lungs have not been observed in other intermediate- and chronic-duration studies of rats or mice orally exposed to trichloroethylene (Maltoni et al. 1986; NCI 1976; NTP 1988, 1990). The maximum doses used in these studies were 3,000 mg/kg/day for an intermediate-duration study in mice (NTP 1990) and 1,097 mg/kg/day for a chronic-duration study in rats (NCI 1976).

Cardiovascular Effects. In one case study, a woman who had accidentally consumed about 20 mL of trichloroethylene was reported to have suffered a myocardial infarction within 2 hours of ingestion (Morreale 1976). In two other case studies, men who ingested 350 and 500 mL of trichloroethylene had ventricular arrhythmias that persisted for up to 3 days (Dhuner et al. 1957). The arrhythmias were described as ventricular tachycardia with extrasystoles from different ventricular foci. Cardiac arrhythmia was also reported in women who ingested unknown amounts of trichloroethylene (Moritz et al. 2000; Perbellini et al. 1991). Sinus tachycardia was observed in a man who ingested approximately 70 mL of trichloroethylene (Brüning et al. 1998) and another man who ingested an unknown amount of trichloroethylene (Vattemi et al. 2005).

Cardiovascular effects of trichloroethylene were investigated in families from Woburn, Massachusetts, that included at least one child with leukemia (Byers et al. 1988). Medical and laboratory tests were conducted on 25 family members who were included in the study. Of those family members who were adults at the time of assessment (apparently 23 of the 25), 14 complained of symptoms including unexplained rapid heart rate at rest, palpitations, or near syncope. Eleven of these adults were given resting and exercise tolerance electrocardiograms, 24-hour Holter monitoring tests, and echocardiograms. Of these 11, 8 had serious ventricular dysfunctions, 7 had multifocal premature ventricular beats, and

6 required cardiac medication. None of the subjects had clinically significant coronary artery disease. No rationale was given for the selection of the 11 adults given extensive testing. No background information on family history of heart disease, smoking habits, or occupational history was given on any of the 25 family members. Other details and limitations of this study are described in Section 3.2.2.7. When compared to a national sample population, statistically significant excess of stroke was consistently reported in the ATSDR Trichloroethylene Subregistry baseline and follow-up reports of persons environmentally exposed to trichloroethylene (ATSDR 1994, 1999; Burg and Gist 1999; Burg et al. 1995; Davis et al. 2005). However, inherent limitations in study design preclude establishment of a cause-and-effect relationship.

Histopathological changes in the heart have not been observed in intermediate- and chronic-duration studies of rats or mice orally exposed to trichloroethylene (Maltoni et al. 1986; NCI 1976; NTP 1988, 1990). The maximum doses used in these studies were 2,000 mg/kg/day for rats and 3,000 mg/kg/day for mice (intermediate-duration studies) (NTP 1990).

Gastrointestinal Effects. Vomiting, diarrhea, hemorrhagic gastritis, and abdominal perforation and necrosis have been reported in people who ingested large amounts of trichloroethylene (De Baere et al. 1997; Liotier et al. 2008; Moritz et al. 2000; Vattemi et al. 2005). Some of the people exposed to trichloroethylene and other chlorinated hydrocarbons in the drinking water in Woburn, Massachusetts, complained of chronic nausea, episodic diarrhea, and constipation (Byers et al. 1988). Although 52% of the subjects had these complaints, these general signs could not be specifically attributed to the trichloroethylene. Study limitations are described in Section 3.2.2.7. Self-reported gastrointestinal problems were not increased among persons in the ATSDR Trichloroethylene Subregistry who were exposed to trichloroethylene in their drinking water (ATSDR 1994, 1999; Burg and Gist 1999; Burg et al. 1995; Davis et al. 2005).

Gas pockets in the intestinal coating and blood in the intestines were observed in five male mice treated with trichloroethylene in drinking water at a dose of 660 mg/kg/day (Tucker et al. 1982). Similar effects were observed in five male mice at a dose of 217 mg/kg/day, with no mice affected at doses of 393 or 18 mg/kg/day. Unfortunately, the number of mice examined for this effect was not clearly stated. Although this effect was not dose-related, it is an interesting observation and appears to be consistent with the human cases of gas-filled cysts in the submucosa of the small intestine observed in persons occupationally exposed to trichloroethylene (Nakajima et al. 1990a) (see Section 3.2.1.2).

Histopathological changes in the gastrointestinal tract have not been observed in intermediate- or chronic-duration studies in which rats and mice were administered trichloroethylene by gavage in corn oil (NCI 1976; NTP 1988, 1990) or olive oil (Maltoni et al. 1986). The maximum doses used in these studies were 2,000 mg/kg/day for rats and 3,000 mg/kg/day for mice (intermediate-duration studies) (NTP 1990).

Hematological Effects. No effects on blood coagulation (Perbellini et al. 1991) or routine hematology tests (Todd 1954) were observed in persons accidently exposed to a single oral dose of trichloroethylene that resulted in coma. When compared to a national sample population, a statistically significant excess of anemia was consistently reported in the ATSDR Trichloroethylene Subregistry baseline and follow-up reports of persons environmentally exposed to trichloroethylene (ATSDR 1994, 1999; Burg and Gist 1999; Burg et al. 1995; Davis et al. 2005). However, inherent limitations in study design preclude establishment of a cause-and-effect relationship. For example, exposures to trichloroethylene were estimated from measured trichloroethylene concentrations in supply wells rather than from water samples from residences. Self-reported symptoms of members of the trichloroethylene subregistry may have been influenced by knowledge of trichloroethylene exposure. Selected symptoms are common to trichloroethylene and other substances found in the water sources.

Hematological effects were not observed in mice treated by gavage with trichloroethylene in 1% aqueous Emulphor for 14 days at doses up to 240 mg/kg/day (Tucker et al. 1982).

ATSDR (2018) is a retrospective cohort study of 50,684 marines stationed at Camp Lejeune, North Carolina who were exposed to drinking water containing tetrachloroethylene, trichlorethylene, and benzene. A reference group consisted of 8,615 marines stationed at Camp Pendleton, California who were not exposed to contaminated drinking water. Trichloroethylene-exposure groups for Camp Lejeune marines were stratified by cumulative exposure tertiles in terms of ppb-months (low: <110; medium: ≤110–<11,030; high: ≥11,030); the number of marines in each tertile was not reported. The Camp Lejeune study population was exposed from 1975 to 1985. The odds of aplastic anemia (23 instances among 50,684 marines at Camp Lejeune; 5 instances among 8,615 marines at Camp Pendleton) were not increased in marines exposed to trichloroethylene in drinking water at Camp Lejeune, North Carolina for any cumulative exposure tertile (ATSDR 2018).

Mice that received 18–793 mg/kg/day trichloroethylene in the drinking water for 6 months showed minor hematological changes, including a 16% decrease in the red blood cell count in males exposed to 660 mg/kg, an increase in fibrinogen levels in males, a decrease in white blood cell counts in females, and

shortened prothrombin times in females (Tucker et al. 1982). These changes were not considered toxicologically significant because they were not dose related, and some effects were transient.

Musculoskeletal Effects. Vattemi et al. (2005) reported skeletal muscle damage in a man who had ingested an unknown amount of trichloroethylene. No other studies were located regarding musculoskeletal effects in humans following oral exposure to trichloroethylene.

No histopathological changes in muscle (Maltoni et al. 1986; NCI 1976; NTP 1988, 1990) or bone (NTP 1988, 1990) have been observed in intermediate- and chronic-duration studies in which rats and mice were treated by gavage with trichloroethylene in corn oil (NCI 1976; NTP 1988, 1990) or olive oil (Maltoni et al. 1986). The maximum doses used in these studies were 2,000 mg/kg/day for rats and 3,000 mg/kg/day for mice (intermediate durations) (NTP 1990).

Hepatic Effects. Hepatic failure was reported in the case of an accidental ingestion of trichloroethylene that led to an acute overdose (Kleinfeld and Tabershaw 1954). In other case studies, blood analyses revealed no hepatic injury in a man who drank several tablespoons of trichloroethylene (Todd 1954) or in women who drank about 20 mL (Morreale 1976) or an unknown quantity (Perbellini et al. 1991). When compared to a national sample population, statistically significant excesses of liver problems were consistently reported in the ATSDR Trichloroethylene Subregistry baseline and follow-up reports of persons environmentally exposed to trichloroethylene (ATSDR 1994, 1999; Burg and Gist 1999; Burg et al. 1995; Davis et al. 2005). However, inherent limitations in study design preclude establishment of a cause-and-effect relationship. For example, exposures to trichloroethylene were estimated from measured trichloroethylene concentrations in supply wells rather than from water samples from residences. Self-reported symptoms of members of the trichloroethylene subregistry may have been influenced by knowledge of trichloroethylene exposure. Selected symptoms are common to trichloroethylene and other substances found in the water sources.

In the retrospective cohort morbidity study of Camp Lejeune, North Carolina marines described in Section 3.2.1.2 (Hematological Effects), ORs for all liver disease were 1.19 (95% CI 0.86–1.64) for the low exposure group, based on 192 instances; 1.63 (95% CI 1.18–2.25) for the medium exposure group, based on 217 cases; and 1.36 (95% CI 0.89–2.07) for the high exposure group, based on 48 instances (ATSDR 2018). ORs for cirrhosis were 1.64 (95% CI 0.78–3.44) for the low exposure group, based on 34 instances; 2.17 (95% CI 1.04–4.53) for the medium exposure group, based on 36 instances; and 1.68 (95% CI 0.62–4.57) for the high exposure group, based on 7 instances. ORs for fatty liver were

1.32 (95% CI 0.91–1.91) for the low exposure group, based on 151 instances; 1.81 (95% CI 1.25–2.63) for the medium exposure group, based on 171 instances; and 1.53 (95% CI 0.95–2.46) for the high exposure group, based on 38 instances. There was no apparent association between exposure to trichloroethylene and risk of hepatomegaly or liver failure.

Substantial toxic effects in the liver have been seen in acute studies in animals. Prout et al. (1985) administered single doses of 10–2,000 mg/kg trichloroethylene to rats and mice. Blood level kinetics of trichloroethylene and its metabolites revealed that trichloroethylene was metabolized more quickly in the mouse, and thus, at high doses, the mouse was exposed to greater concentrations of trichloroethylene metabolites than the rat. Hepatic hypertrophy and centrilobular swelling were observed in mice treated with three daily gavage doses of 2,400 mg/kg trichloroethylene in corn oil; liver effects were not observed in rats similarly treated at 1,100 mg/kg (Stott et al. 1982). Increased relative liver weights and hepatocellular hypertrophy were observed in rats treated by gavage with 1,500 mg/kg/day trichloroethylene in corn oil for 14 days (Berman et al. 1995). A dose-related increase in peroxisomal β-oxidation activity was seen, beginning at 100 mg/kg/day, in mice given trichloroethylene by gavage in corn oil for 10 days, but not in similarly-treated rats at doses up to 2,000 mg/kg/day (Elcombe 1985). A second 10-day study in which rats and mice were treated by gavage with trichloroethylene in corn oil at a dose of 1,000 mg/kg/day has confirmed the observation that the increase in peroxisomal β-oxidation activity is much greater in mice than rats (Goldsworthy and Popp 1987). In rats, relative liver weights and palmitoyl CoA oxidation activity increased 122 and 180%, respectively, while in mice, relative liver weights and palmitoyl CoA oxidation activity increased 150 and 625%, respectively. A similar dosing regimen, up to 1,000 mg/kg/day, produced no change in hepatocyte DNA content in male and female mice, while incorporation of radiolabelled thymidine in whole cells and DNA extracted from mature hepatocytes increased with the dose, responses suggestive of cellular proliferation (Dees and Travis 1993). Peroxisomal beta oxidation and palmitoyl CoA oxidation are markers of peroxisome proliferation. The differences in responses between the rats and mice may reflect species differences in trichloroethylene metabolism.

Several studies showed hepatotoxicity in mice that received trichloroethylene for intermediate periods by gavage in corn oil, although the effects may be sex specific. Males exposed for 6 weeks showed a dose-related progression of hepatic alterations with increasing doses of trichloroethylene, beginning with an increase in the relative liver weight at 100 mg/kg/day and enlarged liver cells and decreased DNA concentration at ≥400 mg/kg/day (Buben and O'Flaherty 1985). This progressed to an increase in the glucose-6-phosphatase activity at 800 mg/kg/day, focal necrosis at 1,600 mg/kg/day, and an increase in

serum ALT activity at 2,400 mg/kg/day. In another study, a dose-related effect was seen in male mice treated with trichloroethylene for 3 weeks (Stott et al. 1982). At 250 and 500 mg/kg/day, there were slight increases in cytoplasmic eosinophilic staining indicative of changes in hepatocyte organelles, while at 1,200 and 2,400 mg/kg/day, there was centrilobular hepatocellular swelling, which included giant cell inflammation and mineralized cells at the highest dose. Trichloroethylene administered to mice at 600 mg/kg/day for 4 weeks produced dose-related hepatic inflammation and associated necrosis in males, but necrosis of the liver was not observed in females treated with doses up to 1,800 mg/kg/day (Merrick et al. 1989). Male mice that received trichloroethylene at 240 mg/kg/day by gavage in 10% Emulphor for 2 weeks, or that consumed drinking water containing as much as 5 mg/mL (equivalent to a dosage of approximately 660 mg/kg/day) for 6 months, showed no treatment-related hepatic effects other than increased liver weights without accompanying macroscopic lesions (Tucker et al. 1982). Although enlarged livers were reported for mice treated by gavage with trichloroethylene in corn oil for 18 months at doses of 1,978 and 1,483 mg/kg/day for males and females, respectively, there were no other indicators of treatment-related liver effects (Henschler et al. 1984). Hepatic effects were not reported in mice treated by gavage with trichloroethylene in corn oil at doses up to 1,739 mg/kg/day for 78 weeks (NCI 1976) or at 1,000 mg/kg/day for 103 weeks (NTP 1990). Liver weight was not increased in female mice administered trichloroethylene in the drinking water for 30 weeks; however, the highest dose tested was 3.5 mg/kg/day (Keil et al. 2009).

Rats appear to be less sensitive than mice to trichloroethylene hepatotoxicity. Daily gavage administration of trichloroethylene (in corn oil) to male rats at 2,000 mg/kg/day for 7 days resulted in 12–16% increased liver weight, but no evidence of treatment-related histopathologic liver lesions (Nunes et al. 2001). Male rats treated with trichloroethylene by corn oil gavage at 1,100 mg/kg/day for 3 weeks failed to exhibit histopathology in the liver, although enhanced hepatic DNA synthesis (175% of control) was detected (Stott et al. 1982). Hepatic effects were not observed in rats treated by gavage with 2,000 mg/kg/day trichloroethylene in corn oil for 13 weeks (NTP 1990). No treatment-related nonneoplastic lesions of the liver were described for male or female rats treated with 1,000 mg/kg/day trichloroethylene for 2 years (NTP 1988, 1990), with 1,097 mg/kg/day for 78 weeks (NCI 1976), or with 250 mg/kg/day for 52 weeks (Maltoni et al. 1986).

Renal Effects. Acute cases of accidental trichloroethylene ingestion revealed no appreciable effects on renal function (Morreale 1976; Perbellini et al. 1991; Todd 1954). One study suggests an association between long-term exposure to solvent-contaminated well water and increased urinary tract infections in children (Lagakos et al. 1986a). However, there was no indication that clinical chemistry testing of urine

samples had been done; such testing might have detected changes in renal function. There was no indication that the increased rates of infection were due to structural or functional renal anomalies. These children were exposed to a number of solvents including trichloroethylene. In another study involving well-water contamination, residents of three communities in Michigan who were exposed to trichloroethylene and other solvents in drinking water had no increase in kidney disease (Freni and Bloomer 1988).

In the retrospective cohort morbidity study of Camp Lejeune, North Carolina marines described in Section 3.2.1.2 (Hematological Effects), ORs for all kidney disease were 1.39 (95% CI 0.90–2.15) for the low exposure group, based on 115 instances; 1.86 (95% CI 1.20–2.87) for the medium exposure group, based on 127 cases; and 1.43 (95% CI 0.81–2.52) for the high exposure group, based on 26 instances (ATSDR 2018). ORs for nephrotic syndrome were 2.68 (95% CI 1.04–6.94) for the low exposure group, based on 31 instances; 2.71 (95% CI 1.03–7.11) for the medium exposure group, based on 25 instances; and 3.03 (95% CI 0.95–9.62) for the high exposure group, based on 7 instances. ORs for renal failure were 1.38 (95% CI 0.75–2.51) for the low exposure group, based on 56 instances; 2.03 (95% CI 1.12–3.68) for the medium exposure group, based on 68 instances; and 1.37 (95% CI 0.62–3.02) for the high exposure group, based on 12 instances.

There was no evidence of nephrotoxicity in mice treated by gavage with trichloroethylene in corn oil at 2,400 mg/kg/day or in rats treated by gavage with 1,100 mg/kg/day for 3 days or 3 weeks (Stott et al. 1982). A gavage dose of trichloroethylene in corn oil (1,000 mg/kg/day) administered to male rats and mice for 10 days resulted in elevated cyanide-insensitive palmitoyl CoA oxidase levels in the kidneys, which is indicative of peroxisomal proliferation but not of cytotoxic effects (Goldsworthy and Popp 1987). In a later report, there was a lack of proximal tubular changes and no increase in alpha-2u-globulin in the kidneys of male rats when 1,000 mg/kg/day trichloroethylene was similarly administered to male and female F344 rats for 10 days (Goldsworthy et al. 1988). Protein droplets and cell replication in males and females did not differ from controls. Kidney weight and urinalyses were normal in mice administered 240 mg/kg/day by gavage in an aqueous Elmuphor solution for 14 days (Tucker et al. 1982). Significantly increased kidney weights (10% higher than controls) and hepatocellular hypertrophy were observed in rats treated by gavage with 1,500 mg/kg/day trichloroethylene in corn oil; significantly increased kidney weights at 5–500 mg/kg/day were only 3–5% higher than controls (Berman et al. 1995). Increased kidney weight and elevated urinary protein and ketones, but no gross pathologic effects, were seen in male rats given 393 mg/kg/day and female rats given 793 mg/kg/day trichloroethylene via drinking water for 6 months (Tucker et al. 1982). Cytomegaly and karyomegaly of the renal tubular epithelial cells were

observed in high-dose rats (males: 2,000 mg/kg/day; females: 1,000 mg/kg/day) and high-dose mice (3,000 mg/kg/day) treated by gavage with trichloroethylene in corn oil for 13 weeks (NTP 1990). The effect was described as minimal to mild in rats and mild to moderate in mice. Because histopathological examinations were not completed at lower doses, this study does not identify a NOAEL for renal effects.

Daily administration of trichloroethylene in corn oil by gavage for 78 weeks to male and female Osborne-Mendel rats (approximately 550–1,100 mg/kg/day) and B6C3F1 mice (approximately 1,200–2,300 mg/kg/day) resulted in treatment-related chronic nephropathy, characterized by degenerative changes in the tubular epithelium (NCI 1976). In chronic (103-week) carcinogenicity studies of rats and/or mice, nonneoplastic renal effects included toxic nephrosis (characterized as cytomegaly) at daily gavage doses of 500 and 1,000 mg/kg (NTP 1990) and cytomegaly of the renal tubular cells coupled with toxic nephropathy (NTP 1988). The NTP (1988) study examined the effects of trichloroethylene in four strains of rats. Osborne-Mendel rats appeared to be the most sensitive to the renal effects of trichloroethylene. At a dose of 500 mg/kg/day, toxic nephrosis occurred in 78% of male and 60% of female Osborne-Mendel rats, 37% of male and 45% female ACI rats, 36% of male and 63% of female Marshall rats, and 20% of male and 17% female August rats. Another chronic study revealed renal tubular nucleocytosis in 50% of male rats exposed to 250 mg/kg/day trichloroethylene for 52 weeks by oil gavage (Maltoni et al. 1986). Further explanation of these studies is in Section 3.2.2.7.

Endocrine Effects. Among persons in the ATSDR Trichloroethylene Subregistry, statistically significant increased prevalence of diabetes was reported at some (but not all) timepoints compared to a national referent population (ATSDR 1994, 1999; Burg and Gist 1999; Burg et al. 1995; Davis et al. 2005). However, inherent limitations in study design preclude establishment of a cause- and-effect relationship. For example, exposures to trichloroethylene were estimated from measured trichloroethylene concentrations in supply wells rather than from water samples from residences. Self-reported symptoms of members of the trichloroethylene subregistry may have been influenced by knowledge of trichloroethylene exposure. Selected symptoms are common to trichloroethylene and other substances found in the water sources.

Adrenal gland weights were not affected in rats treated by gavage with 1,500 mg/kg/day trichloroethylene in corn oil for 14 days (Berman et al. 1995). Histopathological changes in endocrine glands (thyroid, parathyroid, pancreas, adrenals, pituitary) have not been observed in rats or mice exposed by gavage to trichloroethylene in oil for intermediate or chronic durations (Maltoni et al. 1986; NCI 1976; NTP 1988, 1990).

Dermal Effects. Some of the people in Woburn, Massachusetts, who had been chronically exposed to trace amounts of trichloroethylene and other substances in the drinking water reported skin lesions (Byers et al. 1988). These were maculopapular rashes that were said to occur approximately twice yearly and lasted 2–4 weeks. These skin conditions generally ceased 1–2 years after cessation of exposure to contaminated water. The limitations of this study are discussed in Section 3.2.2.7. A case study was published of a 63-year-old rural South Carolina woman exposed to trichloroethylene and other chlorinated hydrocarbons in her well water, who developed diffuse fasciitis, although her husband did not (Waller et al. 1994). The level of trichloroethylene measured in the well water was 19 mg/L. Substitution of bottled water for drinking resulted in improvement of symptoms. Significant excess prevalence of skin rashes, eczema, or other skin disorders was reported in the ATSDR Trichloroethylene Subregistry of people exposed to trichloroethylene from contaminated domestic water supplies at baseline and several follow-up timepoints (ATSDR 1994, 1999; Burg and Gist 1999; Burg et al. 1995; Davis et al. 2005). However, inherent limitations in study design preclude establishment of a cause-and-effect relationship. For example, exposures to trichloroethylene were estimated from measured trichloroethylene concentrations in supply wells rather than from water samples from residences. Self-reported symptoms of members of the trichloroethylene subregistry may have been influenced by knowledge of trichloroethylene exposure. Selected symptoms are common to trichloroethylene and other substances found in the water sources.

Alopecia, roughening of the hair coat, and sores were reported in rats, and alopecia and skin sores were reported in mice treated by gavage with trichloroethylene in corn oil for 78 weeks (NCI 1976). The rats were treated with time-weighted average (TWA) doses of 549 and 1,097 mg/kg/day, and the mice were treated with doses of 1,169 and 2,339 mg/kg/day for males and 869 and 1,739 mg/kg/day for females. Histopathological changes in the skin have not been observed in rats or mice treated by gavage with trichloroethylene in oil for intermediate or chronic durations (Maltoni et al. 1986; NTP 1988, 1990).

Ocular Effects. No studies were located regarding ocular effects in humans following oral exposure to trichloroethylene.

Squinting and a red discharge from the eyes were reported with increasing frequency in rats treated by gavage with trichloroethylene in corn oil at TWA doses of 549 and 1,097 mg/kg/day for 78 weeks (NCI 1976). No histopathological changes were observed in the eyes of rats or mice following chronic-

duration oral treatment with trichloroethylene (Maltoni et al. 1986; NCI 1976; NTP 1988). The highest doses used in these studies were 1,097 mg/kg/day for rats and 2,239 mg/kg/day for mice (NCI 1976).

Body Weight Effects. Several animal studies found no treatment-related effects on body weight during repeated oral exposure to trichloroethylene at gavage doses in the range of 100–3,200 mg/kg/day (Buben and O'Flaherty 1985; Goldsworthy and Popp 1987; Merrick et al. 1989; Stott et al. 1982; Tucker et al. 1982) or through the drinking water at concentrations resulting in estimated doses as high as 206 and 734 mg/kg/day (Griffin et al. 2000a; Waseem et al. 2001).

Several studies reported body weight effects following oral exposure to trichloroethylene; most of these studies did not include information regarding food or water consumption. Mean body weight of a group of rats administered trichloroethylene by gavage at 2,000 mg/kg/day for 13 weeks was 24% lower than that of controls; the NOAEL was 1,000 mg/kg/day (NTP 1990). In pregnant rats treated by gavage at 1,125 mg/kg/day on GDs 6–19, body weight gain was 45% lower than controls (Narotsky and Kavlock 1995). Narotsky et al. (1995) reported 31% lower body weight gain in rats treated with 475 mg/kg/day on GDs 6–15. DuTeaux et al. (2004) reported mean body weight gains of only 18–19 g in groups of male rats receiving trichloroethylene from the drinking water for 14 days at 143 or 270 mg/kg/day; the control group exhibited a mean body weight gain of 78 g. However, nonstatistically significant differences in mean initial body weight may have influenced the weight gain (mean initial body weight of controls was only 553 g compared to 573 and 606 g for the low- and high-dose groups, respectively). Cai et al. (2008) reported 26% decreased body weight gain during the first 11 weeks of a 48-week study in which female mice were administered trichloroethylene in the drinking water at concentrations resulting in an author-estimated average trichloroethylene intake of 60 mg/kg/day; there was no apparent treatment-related effect on water consumption, but the report did not include information regarding food consumption. As much as 30% depressed mean body weight was noted in young mice that received trichloroethylene from the drinking water at 122 mg/kg/day during 4 weeks of postweaning treatment; the mice had also been exposed via their mothers during gestation and lactation (Blossom and Doss 2007). Water consumption was similar among controls and trichloroethylene-treated groups, but food consumption data were not included in the study report. There were no effects on body weight among similarly-treated mice that received trichloroethylene from the drinking water at 31 mg/kg/day (Blossom et al. 2008).

Following chronic exposure, body weights of rats were similar to controls or up to 18% lower than controls at doses of 500 or 1,000 mg/kg/day, respectively (NCI 1976; NTP 1988, 1990). Among the different rat strains tested (ACI, August, Marshall, Osborne-Mendel), one gender was not consistently

more sensitive to the effects of trichloroethylene on body weight than the other gender. Body weights were not affected in rats treated by gavage with trichloroethylene in olive oil at 250 mg/kg/day for 52 weeks (Maltoni et al. 1986). In mice treated by gavage with trichloroethylene in corn oil for 103 weeks, body weights of males were 10% less than controls at a dose of 1,000 mg/kg/day, with no effect on body weights of female mice (NTP 1990). No body weight effects were seen in mice of either sex treated by gavage with trichloroethylene in corn oil for 78 weeks at doses up to 2,339 mg/kg/day (NCI 1976). A 12% depression in mean terminal body weight was noted in a group of male mice administered trichloroethylene in the drinking water for 12 months at a concentration resulting in an estimated trichloroethylene dose of 3.3 mg/kg/day; there were no effects on terminal body weight of similarly-exposed female rats (Peden-Adams et al. 2008). However, these rats had also been exposed to trichloroethylene via their mothers during gestation.

3.2.2.3 Immunological and Lymphoreticular Effects

Immunological abnormalities were reported in 23 of 25 adults in Woburn, Massachusetts, who were exposed to contaminated well water and who were family members of children with leukemia (Byers et al. 1988). These immunological abnormalities, tested for 5 years after well closure, included persistent lymphocytosis, increased numbers of T-lymphocytes, and depressed helper:suppressor T-cell ratio. Auto-antibodies, particularly anti-nuclear antibodies, were detected in 11 of 23 adults tested. This study is limited by the possible bias in identifying risk factors for immunological abnormalities in a small, nonpopulation-based group identified by leukemia types. Other limitations of this study are described in Section 3.2.2.7. A study of 356 residents of Tucson, Arizona, who were exposed to trichloroethylene (6–500 ppb) and other chemicals in well water drawn from the Santa Cruz aquifer found increased frequencies of 10 systemic lupus erythematosus symptoms, 5 of which were statistically significant (arthritis, Raynaud's phenomenon, malar rash, skin lesions related to sun exposure, seizure or convulsions) (Kilburn and Warshaw 1992). Diffuse fasciitis with eosinophilia was reported in a woman who had used well water contaminated with trichloroethylene (14 mg/L) for 6 years (Waller et al. 1994).

In the retrospective cohort morbidity study of Camp Lejeune, North Carolina marines described in Section 3.2.1.2 (Hematological Effects), risks of lupus or scleroderma were not increased in any trichloroethylene cumulative exposure group (ATSDR 2018).

Limited information was located regarding the potential for orally-administered trichloroethylene to induce immunosuppression in laboratory animals. Sanders et al. (1982) administered trichloroethylene to

male and female CD-1 mice by gavage at doses of 24 or 240 mg/kg/day for 14 days and to other groups of mice via the drinking water for 4 or 6 months at concentrations resulting in doses ranging from 18 to 793 mg/kg/day. Significantly decreased cell-mediated immune response to SRBCs was reported in the gavage-treated male (but not female) mice (25–61% decreased relative to controls). All groups of female (but not male) mice exposed via the drinking water exhibited significantly decreased cell-mediated immunity after 4 months of treatment (33–43% decreased relative to controls); however, following 6 months of treatment, the decreased response was observed only in the high-dose (793 mg/kg/day) group of female mice. In the drinking water study, antibody-mediated immunity was significantly inhibited in females only at the two highest doses (437 and 793 mg/kg/day). Overall, females were more sensitive and the effects on the immune system were consistent with those of other chlorinated hydrocarbons. No effects were seen on bone marrow or macrophage function. However, limitations of this study included the lack of a clear dose-response in most of the assays and the transient nature of some of the responses.

The potential for trichloroethylene to accelerate autoimmune diseases has been investigated in several oral studies. The MRL+/+, MRL-*lpr*, and NZB x NZW mouse strains spontaneously develop conditions that resemble the human disease, systemic lupus erythematosus (SLE). The MRL-*lpr* and NZB x NZW strains exhibit a high degree of susceptibility with early disease development (6–8 months); the MRL+/+ strain is less severely affected and exhibits later disease development (12 months). The MRL+/+ strain has been used in most studies.

Keil et al. (2009) administered trichloroethylene in the drinking water to groups of female NZBWF1 mice (known to spontaneously develop autoimmune disease) and B6C3F1 mice (a commonly-used strain used in immunotoxicity testing and not genetically prone to develop autoimmune disease) for 27 or 30 weeks, respectively, at 1.4 or 14 ppm (estimated trichloroethylene doses of 0.35 and 3.5 mg/kg/day, respectively). The B6C3F1 mice exhibited 30–38% decreased thymus weight; this effect was not seen in the autoimmune disease-prone strain. Numbers of activated T-cells (CD4+/CD44+) were increased in the B6C3F1 mice, but not the autoimmune disease-prone strain. Serum levels of autoantibodies to double-stranded DNA (dsDNA) and single-stranded DNA (ssDNA) were increased at more time points in the B6C3F1 mice than the autoimmune disease-prone strain. As expected in the autoimmune disease-prone strain, control mice exhibited age-related steadily increasing levels of antiglomerular autoantibodies; however, significant increases in antiglomerular autoantibodies in the trichloroethylene-treated autoimmune disease-prone strain were observed only at 11 and 19 weeks of age. Trichloroethylene exposure did not affect serum levels of antiglomerular autoantibodies in the B6C3F1 strain. Total serum IgG levels were significantly increased in the autoimmune disease-prone strain at 11 and 36 weeks of age

(high-dose group only) and in the B6C3F1 strain at 26 weeks of age (high-dose group only) and 39 weeks of age (low- and high-dose groups). Trichloroethylene did not significantly alter splenic NK cell activity in either mouse strain. Under the conditions of this study, trichloroethylene did not appear to contribute to the progression of autoimmune disease in the autoimmune disease-prone strain, but may have increased expression of markers associated with autoimmune disease in the B6C3F1 strain. The effect of decreased thymus weight in the low-dose group of mice serves as partial basis for the chronic-duration inhalation and oral MRLs for trichloroethylene (see Appendix A); this immunological effect is considered relevant to humans in the absence of data to indicate otherwise.

Female MRL+/+ mice (Gilbert et al. 1999; Griffin et al. 2000a) were exposed to trichloroethylene in the drinking water for 4, 8, or 22 weeks at concentrations of 0, 2.5, or 5.0 mg/mL (estimated doses of 0, 455, and 734 mg/kg/day, respectively).

After 4 weeks of treatment with trichloroethylene, splenic CD4+ T-cells were found to exhibit a dose-dependent increase in the percentage of cells expressing high levels of CD44, and a corresponding decrease in the percentage of cells expressing low levels of CD45RB; total serum immunoglobulins were increased as well. These results are suggestive of a trichloroethylene-induced accelerated autoimmune response. A subsequent study (Griffin et al. 2000b) employed lower trichloroethylene concentrations (0, 0.1, 0.5, and 2.5 mg/mL; estimated doses of 0, 21, 100, and 400 mg/kg/day) for 4 or 32 weeks and reported significantly increased serum antinuclear antibody levels following 4 weeks of treatment at 0.1 and 0.5 mg trichloroethylene/kg/day, dose-related increased percentage of activated CD4+ T-cells at 32 weeks, and significantly increased hepatic mononuclear infiltration in the portal region (a type of hepatic infiltration consistent with autoimmune hepatitis). These results collectively suggest that trichloroethylene exposure at occupationally-relevant concentrations might accelerate an autoimmune response.

Cai et al. (2008) exposed female MRL+/+ mice to trichloroethylene in the drinking water at 0 or 0.5 mg/mL (estimated doses of 0 or 60 mg/kg/day) for up to 48 weeks and reported increased serum concentrations of antinuclear antibodies after 36 and 48 weeks, accompanied by histopathological evidence of lymphocyte infiltration in the liver at 36 and 48 weeks and in the pancreas, lung, and kidney at 48 weeks. Immunoglobulin deposits were detected in kidney glomeruli at 48 weeks as well. The results suggest that trichloroethylene promoted inflammation in these organs.

Evidence of trichloroethylene-induced enhancement of allergic or hypersensitivity reactions in animals includes results of several studies by Seo and coworkers (Kobayashi et al. 2010, 2012; Seo et al. 2008b, 2012). In these studies, male rats or mice were administered trichloroethylene in the drinking water for 2 or 4 weeks at concentrations resulting in ingested doses of 0.12 µg trichloroethylene/mouse/day (low dose),12 µg/mouse/day (high dose), 0.73 µg/rat/day (low dose), or 72.6 µg/rat/day (high dose). Based on default reference body weights (EPA 1988), estimated doses were 0.004 and 0.4 mg trichloro-ethylene/kg/day for the low- and high-dose mice, respectively, and 0.0024 and 0.24 mg/kg/day for the low- and high-dose rats, respectively. Treatment with trichloroethylene at the lowest doses tested was reported to enhance passive and active anaphylaxis reactions and antigen-stimulated allergic responses and increase splenocyte proliferation, including concentration-related increased percentage of CD8+ cells in ovalbumin-aluminum hydroxide-immunized mice. The low dose levels employed in these studies were ≥2 orders of magnitude lower than those employed in other oral animal studies.

It should be noted that histopathological changes in the spleen and thymus were not observed in rats following acute-duration oral exposure to trichloroethylene in corn oil (Berman et al. 1995) or in rats or mice exposed orally to trichloroethylene for intermediate or chronic durations (Maltoni et al. 1986; NCI 1976; NTP 1988, 1990).

The highest NOAEL values and all LOAEL values from each reliable study for immunological/ lymphoreticular effects in each species and duration category are recorded in Table 3-3 and plotted in Figure 3-17.

Developmental immunotoxicity end points are discussed in Section 3.2.2.6.

3.2.2.4 Neurological Effects

There are several case studies of acute accidental ingestion of varying amounts (2 tablespoons to 16 ounces) of trichloroethylene by humans. These people had muscle weakness, vomiting, and became unconscious or delirious but recovered within 2 weeks (Morreale 1976; Perbellini et al. 1991; Stephens 1945; Todd 1954). Tremor and coma have been observed in people who ingested large amounts (500–1,000 mL) of trichloroethylene (Liotier et al. 2008; Moritz et al. 2000).

The epidemiological studies of the people exposed to trichloroethylene, as well as other chemicals, from well water in Woburn, Massachusetts, did not reveal neurological complaints (study limitations described

in Section 3.2.2.7) (Byers et al. 1988; Lagakos et al. 1986a). Some of the people from this population showed residual damage to the facial and trigeminal nerves, measured by a decreased blink reflex (indicating damage to cranial nerves V and VII) 6 years post-exposure (Feldman et al. 1988). Testing of water supplied to this population over a 2-year period (1979–1981) revealed mean trichloroethylene levels of 256 ppb (range 184–400 ppb) in one well and 111 ppb (range 63–188 ppb) in another well. A limitation of this study is the lack of individual exposure data. A similar limitation was inherent in a study examining neurobehavioral (speed of sway, nonverbal non-arithmetical measure of aptitude, profile of mood states), neurophysiological (simple visual reaction time, body balance, eye closure, and blink), and neuropsychological (immediate recall tests from Wechsler's Memory Scale, pegboard test) test results in residents exposed to well water containing trichloroethylene (6 or 500 ppb) and other chemicals in Tucson, Arizona. In this population, significant decreases in blink reflex, eye closure, choice reaction time, and intelligence test scores, as well as increases in mood disorders, were noted in exposed individuals compared to a group of referents from Phoenix, Arizona (Kilburn and Warshaw 1993). Efforts were made to control for individual variables such as age, sex, income, education, medical and psychological condition, and native language. Further study of this population revealed impaired balance (Kilburn et al. 1994). Among persons in the ATSDR Trichloroethylene Subregistry, statistically significant increases in hearing and speech impairment were noted in children <10 years of age at baseline assessment compared to a national referent population; however, at several follow-up timepoints, significant excesses were not found (ATSDR 1994, 1999, 2002; Burg and Gist 1999; Burg et al. 1995; Davis et al. 2005). The trichloroethylene subregistry study reported borderline statistically significant associations between exposure to trichloroethylene concentrations >15 ppb and signs of neurobehavioral deficits (poorer performance on a digit symbol and contrast sensitivity tests and higher mean scores for confusion, depression, and tension) (ATSDR 2001; Reif et al. 2003). However, there are limitations to the study design. For example, exposures to trichloroethylene were estimated from measured trichloroethylene concentrations in supply wells rather than from water samples from residences. Also, self-reported symptoms may have been influenced by knowledge of trichloroethylene exposure. In a retrospective cohort mortality study of 4,647 full-time civilian workers at Camp Lejeune during 1973–1985 potentially exposed to trichloroethylene-contaminated drinking water (among other contaminants), Bove et al. (2014a) did not calculate SMRs for Parkinson’s disease because less than five cases were observed.

In the retrospective cohort morbidity study of Camp Lejeune, North Carolina marines described in Section 3.2.1.2 (Hematological Effects), there was no indication of increased risk of amyotrophic lateral

sclerosis (ALS), multiple sclerosis, or Parkinson's disease in any trichloroethylene cumulative exposure group (ATSDR 2018).

In animal studies, signs of neurotoxicity and neuropathology have been observed in response to oral doses of trichloroethylene. Note that studies on neurological effects in laboratory animals exposed only during gestation are discussed in Section 3.2.2.6 (Oral Exposure, Developmental Effects).

In acute studies, increased rearing activity was observed in rats treated by gavage with 500 mg/kg/day trichloroethylene in corn oil for 14 days (Moser et al. 1995). Effects on activity were not observed at 150 mg/kg/day. Transient ataxia, observed shortly after dosing, was reported in pregnant rats treated by gavage with 633 mg/kg/day trichloroethylene in corn oil on GDs 6–15 (Narotsky et al. 1995). Ataxia was not observed at 475 mg/kg/day. Adult male rats exposed to 312 mg/L trichloroethylene in their drinking water (approximate dose of 23.3 mg/kg/day) for 4 weeks, followed by 2 weeks of nonexposure, then 2 more weeks of exposure, showed increased performance in the Morris Swim Test and decreased brain myelination (Isaacson et al. 1990). Nunes et al. (2001) reported 25% increased foot splay in rats administered trichloroethylene by gavage (in corn oil) at 2,000 mg/kg/day for 7 days. Degenerative changes in dopaminergic neurons were observed in the substantia nigra from rats administered trichloroethylene by gavage at 1,000 mg/kg/day 5 days/week for 6 weeks; dopamine levels were significantly decreased in the substantia nigra, but not in the striatum (Gash et al. 2008).

Exposures of 10 weeks (5 days/week) to 2,500 mg/kg/day trichloroethylene in corn oil by gavage resulted in altered myelin thickness in the rat mental nerve, a branch of the trigeminal nerve (Barret et al. 1991). Effects of similar exposures on the rat trigeminal nerve included decreased fiber diameter and altered fatty acid composition in total lipid extracts, indicative of demyelination (Barret et al. 1992). Stronger effects were seen with the trichloroethylene decomposition product dichloroacetylene.

Central nervous system effects were also observed during two chronic studies of rats and mice. In the first study, rats exposed to 500 or 1,000 mg/kg/day trichloroethylene in corn oil by gavage for 103 weeks exhibited sporadic and generally transient effects that included ataxia, lethargy, convulsions, and hind limb paralysis (NTP 1988). Later in the study some rats convulsed before dosing and while they were being weighed, suggesting that the effect was more than just an acute effect occurring directly after dosing. In a 54-week carcinogenicity study using exposure levels of 2,400 mg/kg/day for males and 1,800 mg/kg/day for females, mice demonstrated central nervous system effects characterized by an initial period of excitation a few minutes after daily treatment by gavage with trichloroethylene in corn

oil, followed by a subanesthetic state (not characterized) lasting another 15–30 minutes (Henschler et al. 1984).

The highest NOAEL values and all LOAEL values from each reliable study for neurological effects in each species and duration category are recorded in Table 3-3 and plotted in Figure 3-17.

3.2.2.5 Reproductive Effects

Adverse reproductive effects were not noted in a human population in Massachusetts that was exposed to trichloroethylene in drinking water (Byers et al. 1988; Lagakos et al. 1986a). There was no increase in adverse pregnancy outcomes within three communities in Michigan where residents were exposed to trichloroethylene and other solvents in drinking water (Freni and Bloomer 1988). Residents in communities surrounding the Rocky Mountain Arsenal in Colorado were assessed for health outcomes, including selected reproductive/developmental end points, after trichloroethylene was detected in the drinking water (ATSDR 2001). There were no statistically significant positive associations between exposure to trichloroethylene and outcomes that included parity, miscarriages, birth defects, and abnormal menstrual cycle, even within the group with highest estimated exposures to trichloroethylene (>10 ppb). This study is limited for the purpose of determining causal relationships between exposure to trichloroethylene and health outcomes because exposures to trichloroethylene were estimated from measured trichloroethylene concentrations in supply wells rather than from water samples from residences, and self-reported symptoms of members of the trichloroethylene subregistry may have been influenced by knowledge of trichloroethylene exposure.

The retrospective cohort morbidity study of Camp Lejeune, North Carolina marines described in Section 3.2.1.2 (Hematological Effects) evaluated risk of adverse male and female reproductive effects associated with trichloroethylene cumulative exposure from contaminated drinking water sources (ATSDR 2018). ORs for risk of male infertility were 2.69 (95% CI 1.22–5.92) for the low exposure group, based on 64 instances; 2.83 (95% CI 1.28–6.29) for the medium exposure group, based on 54 instances; and 2.31 (95% CI 0.88–6.05) for the high exposure group, based on 11 instances. ORs for risk of low sperm count were 4.26 (95% CI 1.01–17.96) for the low exposure group, based on 29 instances; 4.59 (95% CI 1.08–19.50) for the medium exposure group, based on 25 instances; and 0.74 (95% CI 0.07–8.15) for the high exposure group, based on 1 instance. ORs for risk of female infertility were 1.58 (95% CI 1.05–2.37) for the low exposure group, based on 81 instances; 1.18 (95% CI

0.58–2.39) for the medium exposure group, based on 12 instances; and 1.73 (95% CI 0.83–3.60) for the high exposure group, based on 12 instances.

A continuous breeding fertility study was conducted in which male and female F344 rats were fed diets containing microencapsulated trichloroethylene that resulted in doses of approximately 0, 75, 150, or 300 mg/kg/day from 7 days before mating through birth of the F2 generation (NTP 1986). There was an increase in the relative left testis/epididymis weight in the F0 generation and a decrease in absolute left testis/epididymis weight in the F1 generation; however, the NTP staff concluded that these results were more likely due to generalized toxicity rather than a specific effect on the reproductive system. Furthermore, the testis/epididymis weight changes were not accompanied by histopathological changes in these or any other tissue examined. There was no effect on reproductive performance. A similarly designed fertility study was conducted with CD-1 mice using the same dietary concentrations of trichloroethylene (up to 750 mg/kg/day) (NTP 1985). There were no treatment-related effects on mating, fertility, and reproductive performance in either the F0 or F1 mice, but sperm motility was reduced by 45% in F0 males and 18% in F1 males. F1 males exhibited significantly increased mean relative left testis/epididymis and right epididymis weights (9–11% greater than controls).

No effects on female fertility were noted in rats treated by gavage with trichloroethylene in corn oil at 1,000 mg/kg/day for 2 weeks before mating through gestation and postnatal days 0–31 (Manson et al. 1984). Maternal body weight gain was about 9% lower than controls at 1,000 mg/kg/day. No treatment-related effects on fertility were seen in studies of female rats receiving trichloroethylene from the drinking water during premating and/or gestation at estimated doses as high as 129 mg/kg/day (Dawson et al. 1993; Johnson et al. 1998, 2003). DuTeaux et al. (2004) reported decreased *in vitro* fertilization capacity of sperm from male rats that had been exposed to trichloroethylene in the drinking water for 14 days at concentrations resulting in estimated doses of 143 and 270 mg/kg/day. There were no significant effects on reproductive organ weights, sperm concentration, or percentage of motile sperm, although histopathologic evaluations of testes revealed slight (unspecified) changes in efferent ductile epithelium. Zenick et al. (1984) reported impairment in copulatory behavior, mount/ejaculation latency, and intromissions in male rats administered trichloroethylene by gavage at 1,000 mg/kg/day, 5 days/week for 6 weeks.

Histopathological changes in reproductive organs were not observed in rats or mice treated by gavage with trichloroethylene in corn oil for chronic durations (Maltoni et al. 1986; NCI 1976; NTP 1988, 1990).

The highest doses used in these studies were TWA doses of 1,097 mg/kg/day in rats, 2,239 mg/kg/day in male mice, and 1,739 mg/kg/day in female mice (NCI 1976).

The highest NOAEL values and all LOAEL values from each reliable study for reproductive effects in each species and duration category are recorded in Table 3-3 and plotted in Figure 3-17.

3.2.2.6 Developmental Effects

Epidemiological data are typically limited by concomitant exposure to other potentially hazardous substances, and case-control studies are limited by small numbers of cases.

In a survey of 80,938 live births and 594 fetal deaths conducted in an area of New Jersey with contaminated public drinking water (average exposure of 55 ppb), Bove et al. (1995) reported ORs for trichloroethylene in the drinking water and risk of selected developmental end points. For exposure to trichloroethylene at levels >10 ppb, ORs were 1.68 (90% CI 0.76–3.52) for central nervous system defects based on six cases, 2.53 (90% CI 0.91–6.37) for neural tube defects based on four cases, 1.30 (90% CI 0.39–3.68) for oral cleft defects based on three cases, 1.24 (50% CI 0.75–1.94) for major cardiac defects based on an unspecified number of cases, and 1.30 (50% CI 0.88–1.87) for ventricular septal defects based on an unspecified number of cases. Uncertainty regarding exposure classification and small numbers of cases, in addition to the presence of other drinking water contaminants, were the main limitations of this study.

In a study of residents exposed to drinking water contaminated with solvents (including 267 ppb trichloroethylene) in Woburn, Massachusetts, there was a suggestion that the combination of eye and ear anomalies and the combination of central nervous system, chromosomal, and oral cleft anomalies in newborns were associated with contaminated water exposure (Lagakos et al. 1986a). However, several scientists have questioned the biological relevance of the unusual groupings of these anomalies for purposes of statistical analysis (MacMahon 1986; Prentice 1986). The grouping of central nervous system disorders, chromosomal disorders, and oral cleft anomalies is questionable because they are not linked in embryological development. Other disorders that the study authors classified as congenital are not so classified by the International Classification of Diseases (ICD). Because expected rates are generated from statistical databases that rely on the ICD classifications, this regrouping could affect the data analyses and the conclusions drawn from them. In addition, not enough demographic or medical background information was provided on the subjects in this study to indicate that other potential

contributing factors were being considered. The study was performed following considerable publicity about the well contamination and the possible health effects that could follow these exposures, thus potentially contributing to recall bias of the participants. Further limitations of this study are described in Section 3.2.2.7.

In a report of the Woburn population prepared by the Massachusetts Department of Public Health (MDPH 1996), it was indicated that there was an increased prevalence in choanal atresia (a rare respiratory effect) and hypospadias/congenital chordee, and a small increase in eye defects, but there was no association between trichloroethylene exposure and heart defects. There were no statistically significant associations between exposure concentrations and birth defects, although analyses were limited by the small number of cases observed. Birth weights tended to be lower in trichloroethylene-exposed infants compared to controls, but not statistically significantly lower. The rate of choanal atresia per 1,000 live births and fetal deaths was 0.88 in the trichloroethylene-exposed Woburn population (based on 4 cases), compared to rates of 0.11 in the Atlanta comparison population (based on 17 cases) and 0.13 in the California comparison population (based on 33 cases). In a prospective study completed after well closure, the rate of choanal atresia was 0.88 (based on 1 case) in Woburn, 0.11 (based on 1 case) in the surrounding communities, and 0.2 in Atlanta (based on 9 cases) and 0.13 in California (based on 33 cases) (MDPH 1996). The study authors cautioned that their study did not rule out moderate increases in rates of the less common adverse reproductive outcomes. For these outcomes only large increases would have been detected.

White et al. (1997) reported verbal naming/language impairment in 6/13 children from the Woburn, Massachusetts population and similar indicators of cognitive impairment in children from two other communities with reported high levels of trichloroethylene in the drinking water (from 3.3 ppb to as much as 2,440 ppb) for as long as 12–25 years. However, these results are based on clinical examination and diagnostic procedures performed on limited numbers of subjects.

In a Tucson, Arizona, population exposed to trichloroethylene (6–239 ppb) and other contaminants (dichloroethylene and chromium) in the drinking water from certain wells, an association was found between the elevated levels of trichloroethylene in drinking water and congenital heart disease in children whose parents were exposed during the month before conception and the first trimester of pregnancy (Goldberg et al. 1990). Among children whose mothers lived in the areas receiving trichloroethylene contaminated water during the first trimester of pregnancy, the rate of congenital heart defects was approximately 2.5 times higher than among children of mothers who were not exposed to trichloro-

ethylene during pregnancy. Moreover, the rate of congenital heart defects decreased in the previously exposed area after the contaminated wells were shut off. The cases of birth defects reported in this study were medically confirmed and all were derived from the same hospital clinic population. A significant limitation of this report is that the exposure was ill-defined. Exposures for individuals were not quantifiable, the areas that received trichloroethylene-contaminated water were not clearly delineated, the year when exposure began was unknown, and the amount of trichloroethylene in the water varied from year to year, though actual concentrations were measured in 1981. In addition, the population was exposed to other substances in the water (including dichloroethylene and chromium), although concentrations of trichloroethylene were highest. Rodenbeck et al. (2000) found no significant association between trichloroethylene in the drinking water and birth weight outcomes in a section of the Tucson, Arizona, area where the trichloroethylene contamination in the drinking water was estimated to have ranged from <5 to 107 μg/L during the period of 1978–1981. In this study, a comparison group without trichloroethylene-contaminated drinking water was selected to match the socioeconomic status of the trichloroethylene-exposed population.

Among persons in the ATSDR Trichloroethylene Subregistry, statistically significant increases in hearing and speech impairment were noted in children <10 years of age at baseline assessment compared to a national referent population; however, at several follow-up timepoints, significant excesses were not found (ATSDR 1994, 1999, 2002; Burg and Gist 1999; Burg et al. 1995; Davis et al. 2005). There are inherent limitations to the ATSDR Trichloroethylene Subregistry study. For example, exposures to trichloroethylene were estimated from measured trichloroethylene concentrations in supply wells rather than from water samples from residences. Self-reported symptoms of members of the trichloroethylene subregistry may have been influenced by knowledge of trichloroethylene exposure. Selected symptoms are common to trichloroethylene and other substances found in the water sources.

A small effect on birth weight was noted in a report on adverse birth outcomes for a population living at Camp Lejeune, North Carolina (ATSDR 1997, 1998). The women were exposed some time during gestation. Statistical significance ($p \leq 0.05$) was achieved for all births (n=31) within the trichloroethylene-exposed group (mean birth weight 3,361 kg; standard error [SE] 71.8) compared to 997 unexposed births (mean birth weight 3,469 kg; SE 16.9) and all male births (trichloroethylene-exposed mean birth weight 3,213 kg; SE 113.2; n=12 versus trichloroethylene-unexposed birth weight 3,527 kg; SE 25.2; n=497). The trichloroethylene-exposed female birth weight (n=19) was not significantly different from that of controls (n=500). The study authors cautioned that the small trichloroethylene-exposed group size weakens the causal association. In a case-control study of children

born to mothers exposed to trichloroethylene-contaminated drinking water at Camp Lejeune during pregnancy in the time period of 1968–1985, exposure to trichloroethylene at >5 ppb resulted in ORs of 2.4 (95% CI 0.6–9.6) for risk of neural tube defects based on 3 cases in the exposed group and 0.8 (95% CI 0.2–3.0) for risk of oral cleft defects based on three cases in the exposed group (Ruckart et al. 2013).

A case-control study examining maternal residential proximity to chlorinated solvent emissions was conducted using the Texas Birth Defects Registry for births occurring between 1996 and 2008 (Brender et al. 2014). For trichloroethylene adjusted ORs (95% CIs) for neural tube defect, anencephaly, and spina bifida were 0.95 (0.82, 1.08), 0.99 (0.76, 1.29), and 0.94 (0.79, 1.12), respectively. These risk estimates were not adjusted for exposure to other solvents.

A study of three Michigan communities exposed to chlorinated solvents including trichloroethylene (up to 14,890 ppb) in contaminated drinking water found no increase in congenital defects (Freni and Bloomer 1988). The size of the cohort, however, was smaller than that of other studies.

Gilboa et al. (2012) evaluated possible associations between estimated maternal occupational exposure to various solvents (including trichloroethylene) and congenital heart defects in offspring. The study population included mothers (n=2,047) of infants with simple isolated congenital heart defects and control mothers (n=2,951) who delivered between 1997 and 2002 and who participated in the National Birth Defects Prevention Study. Occupational solvent exposure was estimated based on self-reported information regarding job description and possible chemical exposures. There was no difference in prevalence of congenital heart defects among trichloroethylene-exposed mothers and control mothers (69/2047 or 3.4% among case mothers versus 94/2951 or 3.2% among control mothers; p=0.6). Major limitations of this study include the potential for misclassification of exposure and confounding by exposure to other solvents.

Bukowski (2014) reviewed available epidemiological data and noted that four studies reported associations between trichloroethylene exposure and congenital heart defects (Bove et al. 1995; Forand et al. 2012; Goldberg et al. 1990; Yauck et al. 2004). Bukowski (2014) stated that these studies contained inherent limitations in study design or analytical procedures, which may have influenced the findings. Bukowski (2014) also identified five studies that found no association between exposure to trichloroethylene and congenital heart defects (Gilboa et al. 2012; Lagakos et al. 1986a; MDPH 1996; Ruckart et al. 2013; Tola et al. 1980). Based on the available epidemiological data, Bukowski (2014)

contended that there is “no substantive or consistent evidence” for trichloroethylene-induced congenital heart defects.

Studies in animals indicate that trichloroethylene can act as a developmental toxicant, especially at doses high enough to result in maternal toxicity. Significant decreases in litter size have been reported in rats treated by gavage with 1,125 mg/kg/day trichloroethylene in corn oil on GDs 6–19 in F344 rats (Narotsky and Kavlock 1995) or GDs 6–15 in Sprague-Dawley rats (Narotsky et al. 1995). The deaths appeared to have occurred early in the dosing period. Maternal effects noted at 1,125 mg/kg/day included decreased body weight gain, transient ataxia, and decreased motor activity (Narotsky and Kavlock 1995; Narotsky et al. 1995). A dose-related increase in micro- or anophthalmia that was statistically significant at 1,125 mg/kg/day was also observed (Narotsky et al. 1995). Eye defects were observed in 1, 5.3, 9.2, 11.7, and 30% of pups from dams treated at 0, 475, 633, 844, and 1,125 mg/kg/day, respectively; doses ≥633 mg/kg/day resulted in overt maternal toxicity, including ataxia and significant weight loss (Narotsky et al. 1995). In a study in mice that did not use maternally toxic doses, no developmental effects were observed in the offspring of B6C3F1 mice treated by gavage with 240 mg/kg/day trichloroethylene in corn oil on GDs 1–5, 6–10, or 1–15 (Cosby and Dukelow 1992).

In a continuous breeding study in which trichloroethylene in microcapsules was added to the diet, there was a 61% perinatal mortality rate in F1 offspring of CD-1 mice exposed to 750 mg/kg/day from conception through weaning (NTP 1986). Decreased maternal body weight gain and reduced fetal body weights were also observed, but there were no skeletal or visceral anomalies. F344 rats similarly exposed to 300 mg/kg/day exhibited maternal toxicity manifested as decreased body weight, increased liver and kidney weights, and a slight reduction in litter size with no anomalies (NTP 1986).

Manson et al. (1984) administered trichloroethylene to female rats by gavage in corn oil at 0, 10, 100, or 1,000 mg/kg/day for 2 weeks prior to mating (5 days/week), during 1 week of mating (5 days of treatment), and throughout gestation. Significant treatment-related effects were limited to the 1,000-mg/kg/day group. Maternal effects included the death of 4/23 of the dams and 34% depression of body weight gain among the survivors. One high-dose dam had a completely resorbed litter. Developmental effects included increased numbers of stillborn pups (9/142 including 1/64 males and 8/78 females versus 2/181 controls including 1/87 males and 1/94 females). Significantly decreased neonatal survival postculling (postnatal days 3–18) was noted (24/110 deaths including 7 male and 17 female pups versus 14/128 controls including 7/62 males and 7/66 females). These effects on the pups

were likely the result of serious maternal toxicity rather than a direct developmental effect. There were no signs of treatment-related teratogenic effects.

Johnson and coworkers (Dawson et al. 1993; Johnson et al. 1998, 2003) reported increased incidences of cardiac malformations in fetuses of rat dams exposed to trichloroethylene in the drinking water during premating and gestation or gestation alone. Groups of 9–39 female rats were exposed to trichloroethylene in drinking water at 0, 1.5, or 1,100 ppm (estimated doses of 0.218 and 129 mg/kg/day, respectively) either before pregnancy (for 3 months prior to mating), before and during gestation (2 months prior to mating plus 21 days of gestation), or during gestation only (Dawson et al. 1993; Johnson et al. 1998). Maternal toxicity was not observed in any of the exposure groups. Fetal heart defects were not observed in fetuses from dams exposed only before pregnancy. Abnormal fetal heart development was observed at both concentrations in dams exposed before and during pregnancy (3% of 238 concurrent control fetuses; 8.6% or 22/255 of the low-dose fetuses; 9.2% or 40/434 of the high-dose fetuses). In dams exposed only during pregnancy, fetal heart defects were observed only at the higher dose (11/105 or 10.48% versus 3% of 238 concurrent controls).

Johnson et al. (2003) reported results from rat dams administered trichloroethylene in the drinking water at 0.0025, 0.25, 1.5, or 1,100 ppm during gestation (estimated doses of 0.00045, 0.048, 0.218, and 129 mg/kg/day, respectively). The study authors stated that there were no statistically significant differences between controls and trichloroethylene-treated groups regarding maternal and fetal variables other than congenital cardiac abnormalities. Control data were pooled from multiple studies; the study report did not include concurrent control data. Incidences of control fetuses with cardiac abnormalities were 13/606 (2.15%). Incidences of fetuses with cardiac abnormalities in the 0.0025, 0.25, 1.5, and 1,100 ppm groups were 0/144 (0%), 5/110 (4.5%), 9/181 (5.0%), and 11/105 (10.48%), respectively. Compared to the pooled controls, the incidences of fetuses with cardiac abnormalities were significantly increased only at the 1.5 and 1,100 ppm exposure levels ($p=0.044$ and $p<0.001$, respectively). The study authors also reported results on a per-litter basis (number of litters with at least one fetus that exhibited a cardiac malformation per number of litters). Nine of 55 control litters had one or more fetuses with a cardiac malformation; incidences in the 0.0025, 0.25, 1.5, and 1,100 ppm groups were 0/12 (0%), 4/9 (44%), 5/13 (38%), and 6/9 (67%), respectively. Limitations to the studies of Johnson and coworkers include statistical analyses of findings on a per-fetus basis and use of nonconcurrent control data in the analysis.

In comparing the study reports of Dawson et al. (1993) and Johnson et al. (2003), Hardin et al. (2004) noted that: (1) the data for the 1.5 and 1,100 ppm dose groups were common to both studies, (2) there was some variation between the two study reports regarding incidence data for selected cardiac defects, and (3) the report of Johnson et al. (2003) included an "uncharacteristically large control group" (55 dams) compared to 9–13 dams in trichloroethylene-treated groups. Johnson et al. (2004) acknowledged that the data for the 1.5 and 1,100 ppm dose groups were common to both study reports (Dawson et al. 1993; Johnson et al. 2003), and noted that additional dose groups (0.0025 and 0.25 ppm groups) were subsequently assessed in ongoing investigations and included in combination with the 1.5 and 1,100 ppm dose groups to avoid duplication and sacrifice of additional animals. In the Johnson et al. (2003) study report, reclassification of cardiac defects resulted in slight differences from the Dawson et al. (1993) report regarding terminology and incidences for cardiac defects. Ranges of study dates and numbers of animals used in control and trichloroethylene-treated groups were presented in a table published in the correspondence section of the January 2005 Environmental Health Perspectives [113(1):A18] along with explanation for combining results for multiple control groups (Anonymous 2005). In the correspondence section of the April 2014 Environmental Health Perspectives [122(4):A94], it was noted that: (1) exact exposure start dates for two trichloroethylene exposure groups and their concurrent controls in the table published in the correspondence section of the January 2005 Environmental Health Perspectives [113(1):A18] could not be confirmed but were in 1994 (not 1995); (2) all trichloroethylene exposures lasted throughout gestation; (3) all experiments were run with concurrent controls; and (4) rats were ordered on a 40-animal maximum capacity and were randomly assigned to study groups (Anonymous 2014). Critical review of the studies of Johnson and coworkers (Dawson et al. 1993; Johnson et al. 1998, 2003) has led some investigators to conclude that the weight of evidence from human and animal data does not support a role for trichloroethylene in congenital heart defects (e.g., Hardin et al. 2004, 2005; Watson et al. 2006). However, in the absence of convincing information to the contrary, the report of trichloroethylene-induced cardiac malformations in rat fetuses is considered valid and relevant to humans, based on available epidemiological and animal data, as well as mechanistic information (EPA 2011e). EPA (2014a) released results from a Toxic Substances Control Act (TSCA) Work Plan Chemical Risk Assessment for trichloroethylene that included a weight-of-evidence analysis for fetal cardiac malformations following trichloroethylene exposure (see Appendix N in EPA 2014a; see also EPA 2014b). EPA concluded that "while the Johnson et al. studies have limitations, there is insufficient reason to dismiss their findings, especially when the findings are analyzed in combination with the remaining body of human, animal and mechanistic evidence" (see p. 98 in EPA 2014a). An EPA executive panel (EPA 2016) reviewed EPA's position regarding the weight-of-evidence for trichloroethylene-induced fetal cardiac malformations in rats and concluded that the information

presented in the Toxicological Review of Trichloroethylene (EPA 2011e) is "consistent with EPA's IQG [Information Quality Guideline] standards of objectivity and utility." The increased incidences of fetuses with cardiac malformations from the rat dams administered trichloroethylene during gestation serve as partial basis for the chronic-duration inhalation and oral MRLs for trichloroethylene (see Appendix A).

Fisher et al. (2001) designed a study to assess the ability of trichloroethylene and two of its metabolites (TCA and dichloroacetic acid [DCA]) to induce cardiac defects in Sprague-Dawley rat fetuses. Rat dams were administered trichloroethylene by gavage (in soybean oil vehicle) on GDs 6–15 at doses of 0 or 500 mg/kg/day; a positive control group was administered retinoic acid. The metabolites, TCA and DCA, were administered at a 300 mg/kg/day dose level. Fetal hearts were examined on GD 21 by *in situ* cardiovascular stereomicroscope examination, followed by implementation of a special heart dissection and staining method to enhance microscopic visualization of heart morphology. The incidences of fetuses with heart malformations were 13/290 (4.5%) for the trichloroethylene-treated group and 24/367 (6.5%) for the controls. On a litter basis, 12 of 20 litters from the trichloroethylene-treated dams exhibited at least one cardiac malformation compared to 12 of 25 control litters. Incidences of fetuses with heart malformations in the groups administered TCA or DCA were similar to that of controls; the positive control group exhibited expected results (51/155 fetuses with malformations compared to 13/290 controls; 92% of litters with a malformation compared to 60% in controls).

Blossom and Doss (2007) assessed the effects of trichloroethylene on the immune system of young MRL+/+ mice that had been exposed via their mothers during gestation and lactation (maternal doses of 123 and 684 mg/kg/day) and for an additional 4 weeks via their drinking water (offspring doses of 122 and 553 mg/kg/day). Significantly increased cytokine IFN-γ production by splenic CD4+ cells, decreased splenic CD8+ and B220+ lymphocytes, increased IgG2a and histone, and altered thymocyte profiles were observed at the low-dose level. At the high dose, increased IFN-γ production by splenic CD4+ cells; decreased splenic CD+4, CD8+, and B220+ lymphocytes; and altered thymocyte profiles were noted. In a subsequent study that employed a single trichloroethylene exposure level (0.1 mg/mL) resulting in a 25.7 mg/kg/day maternal dose and a 31 mg/kg/day dose to the offspring, trichloroethylene treatment resulted in altered immunoregulation as evidenced by increased thymocyte cellularity associated with increased thymocyte subset distribution, increased reactive oxygen species generation in total thymocytes, and increased splenic CD4+ T-cell production of cytokines IFN-γ and IL-2 in females and TNF-α in males (Blossom et al. 2008).

Peden-Adams et al. (2006) administered trichloroethylene to male and female B6C3F1 mice (not prone to autoimmune disease) via the drinking water at 0, 1.4, or 14 ppm during mating, gestation, and lactation (estimated doses to the dams of 0, 0.37, and 3.7 mg/kg/day). Selected pups were assessed at 3 weeks of age for effects on the immune system (thymus and spleen weights, splenic lymphocyte proliferation, NK cell activity, plaque-forming cell [PFC] response to SRBC, numbers of splenic B220+ cells, and thymic and splenic T-cell immunophenotypes). Other pups were similarly assessed at 8 weeks of age with additional assessments of autoantibodies to dsDNA and delayed-type hypersensitivity response (indicated by foot pad swelling following subcutaneous injection of SRBC). Thymus weights were not affected by trichloroethylene exposure. Spleen weight was depressed by 15% in the 1.4-ppm exposure group of pups 3 weeks of age. Splenic lymphocyte proliferation and NK cell activity were not affected in pups at either tested time point. The PFC response was significantly decreased in male and female pups at both trichloroethylene exposure levels. Splenic numbers of B220+ cells were decreased only in 3-week-old pups of the 14 ppm treatment level. Delayed-type hypersensitivity response was significantly increased in 8-week-old female pups of low- and high-dose groups and in high-dose male pups; there was no significant effect on autoantibodies to dsDNA in the 8-week-old male or female pups. The decreased PFC response in the male and female pups serves as partial basis for the chronic-duration oral MRL for trichloroethylene (see Appendix A); this effect is considered relevant to humans in the absence of data to indicate otherwise.

Postnatal exposure of male mice to 50 or 290 mg/kg/day trichloroethylene between the ages of 10 and 16 days resulted in a significant reduction in rearing (raising front legs, resting on haunches) rate at both doses when they were tested at age 60 days; the effect did not appear to be dose-dependent and there was no treatment-related effect on locomotion or total activity (Fredriksson et al. 1993). The results of this study indicate that trichloroethylene may affect brain maturation.

Results of several animal studies implicate the hippocampal brain region (a region involved in spatial memory and navigation) as a target of trichloroethylene developmental toxicity following gestational and/or early postnatal exposure. A 40% decrease in the number of myelinated fibers was observed in the hippocampus of 21-day-old offspring of rats receiving trichloroethylene from the drinking water at approximately 37 or 75 mg/kg/day from premating throughout gestation and lactation (Isaacson and Taylor 1989). Decreased numbers of myelinated fibers were noted in the hippocampus of young rats receiving trichloroethylene from the drinking water at 5.5 mg/kg/day for 4 weeks (Isaacson et al. 1990); in those rats exposed for 2 additional weeks (following a 2-week non-treatment period) at an effective dose level of 8 mg/kg/day, increased level of performance of spatial navigational tasks and decreased

amount of hippocampal myelin were observed. Decreases in myelinated fibers represent a serious adverse effect. The study authors suggested that the reduction in hippocampal myelin may be related to the increased level of performance of spatial navigational tasks. Blossom et al. (2012) reported altered glutathione redox homeostasis (indicating a more oxidized state) and dose-related increased levels of glutathione precursors within the hippocampus of male mice receiving trichloroethylene via their mothers during lactation and directly from the drinking water for 3 weeks postweaning at estimated doses as low as 2.7 mg/kg/day (postweaning dose); neurobehavioral end points were not assessed. A significant dose-related trend for increased time required for grid traversal was noted in 21-day-old rats that had been exposed to trichloroethylene via their mothers during gestation and lactation at maternal doses ranging from approximately 75 to 300 mg/kg/day (NTP 1986); effects on other measures of open-field locomotor activity or miscellaneous behavior were not observed and evaluation of the F1 rats at 45 days of age was unremarkable, suggesting that trichloroethylene had a transient effect. In contrast, 6-week-old offspring of mice exposed throughout gestation to trichloroethylene in drinking water had increased motor activity, based on the distance traveled in 20 minutes (Blossom et al. 2017). The distance traveled by offspring of dams exposed to a daily dose of 2.96 mg/kg/day was increased by approximately 31% (p=0.01), relative to controls. For dams exposed to 26.56 mg/kg/day, the distance traveled was increased by 21% relative to control; however, this increase did not reach statistical significance (p-0.06). Distance traveled at 2-minute epoch during the 20-minute testing period was significantly increased in offspring of both treatment groups. Results suggest that neurotoxic effects may be sustained in offspring following prenatal-only exposure.

Glucose uptake by the brain was reduced in 21-day-old offspring of rats provided with 312 mg/L trichloroethylene (about 37 mg/kg/day) (Noland-Gerbec et al. 1986). Activity measurements showed increases in the 60-day-old offspring of rats provided with trichloroethylene in the drinking water at 312 mg/L (about 37 mg/kg/day) (Taylor et al. 1985).

The highest NOAEL values and all LOAEL values from each reliable study for developmental effects in each species and duration category are recorded in Table 3-3 and plotted in Figure 3-17.

3.2.2.7 Cancer

Cancer Classifications. Cancer classifications for trichloroethylene by the HHS (NTP 2016), IARC (2014), and EPA (2011e) are reviewed in Section 3.2.1.7 (Inhalation, Cancer). Conclusions made in

comprehensive reviews (EPA 2011e; IARC 2014; NTP 2016) regarding associations between trichloroethylene exposure and specific cancer types also are summarized.

Epidemiological Studies. Epidemiological studies on the potential carcinogenic effects of oral exposure to trichloroethane are of populations exposed to drinking water contaminated with trichloroethylene and other solvents and chemicals, including tetrachloroethylene, benzene, chloroform, arsenic, and other halogenated solvents. The epidemiological data for oral exposure to trichloroethylene are much more limited than the inhalation data due to small numbers of studies and small cohort sizes, as well as potential confounding by co-exposure to other chlorinated solvents. Table 3-4 provides an overview of selected epidemiological studies, including study populations, exposure assessments (qualitative versus semi-quantitative, assessment methods), consideration of confounders, and study strengths and limitations.

Studies were selected for inclusion based on the following considerations:

- studies meeting the following criteria as listed in EPA (2011e): cohort or case-control study design; evaluation of incidence or mortality; adequate selection in cohort studies of exposure and control groups and of cases and controls in case-control studies; trichloroethylene exposure potential inferred to each subject and quantitative assessment of trichloroethylene exposure assessment for each subject by reference to industrial hygiene records indicating a high probability of trichloroethylene use, individual biomarkers, job-exposure matrices, or obtained from subjects using questionnaire (case-control studies);
- studies meeting the EPA (2011e) criteria that were published after 2011; and
- studies reporting risk estimates specific for trichloroethylene.

Five studies met these criteria (Table 3-4): three cohort studies (Bove et al. 2014a, 2014b; Cohn et al. 1994) and two case-control studies (Ruckart et al. 2013, 2015). Military personnel and civilians from the Marine Corps Base at Camp Lejeune, North Carolina were evaluated by ATSDR (2018), Bove et al. (2014a, 2014b), and Ruckart et al. (2013, 2015). The Ruckart et al. (2013) study examined childhood hemopoietic cancers in children exposed prenatally and in early childhood. One study examined a population of adults from New Jersey (Cohn et al. 1994). Several other studies evaluated the carcinogenic potential of drinking water contaminated with trichloroethylene; however, risk estimates specific for trichloroethylene were not reported (Costas et al. 2002; Davis 2005; Fagliano et al. 1990; Freni and Bloomer 1988; Lagakos et al. 1986b; MDPH 1997; Parker and Rosen 1981; Vartiainen et al. 1993). Therefore, these studies were not selected for review. For additional details and reviews of

Table 3-4. Overview of Epidemiological Studies Evaluating Associations between Oral Trichloroethylene and Cancer

Reference; population	Exposure assessment	Confounders considered	Strengths and limitations[a]
Cohort studies			
ATSDR 2018 Camp Lejeune, North Carolina; military personnel	Historical reconstruction of drinking water levels using groundwater fate and transport and water-distribution system models	Sex, age at diagnosis	Strengths[b]: very large cohort of marines (n=50,684); small percentage of loss to follow-up; rigorous reconstruction of historical levels of drinking water contamination; confirmation of diagnosis decreased over-reporting bias Limitations[b]: number of participants in each exposure category was not reported; exposure misclassification bias; data on water consumption were not collected
Bove et al. 2014a; Camp Lejeune, North Carolina; military personnel	Historical reconstruction of drinking water levels using groundwater fate and transport and water-distribution system models	Age; sex; race; calendar period	Strengths[b]: large cohort; small percentage of loss to follow-up; rigorous reconstruction of historical levels of drinking water contamination. Limitations[b]: exposure misclassification bias; disease misclassification bias
Bove et al. 2014b; Camp Lejeune, North Carolina; Civilian employees	Historical reconstruction of drinking water levels using groundwater fate and transport and water-distribution system models	Age; sex; race; calendar period	Strengths[b]: small percentage of loss to follow-up; rigorous reconstruction of historical levels of drinking water contamination Limitations[b]: exposure misclassification bias; lack of information on water usage; small numbers of some cancers resulted in wide confidence intervals; not possible to evaluate exposure-response relationships due to small incidence numbers; lack of information on smoking and other risk factors
Cohn et al. 1994; New Jersey; adults	Qualitative; exposure potential based on water monitoring data	Sex; age	Strengths: none reported Limitations: lack of adjustment for possible confounders; potential misclassification of exposure; lack of information on individual exposure potential

Table 3-4. Overview of Epidemiological Studies Evaluating Associations between Oral Trichloroethylene and Cancer

Reference; population	Exposure assessment	Confounders considered	Strengths and limitations[a]
Case-control studies			
Ruckart et al. 2013; Camp Lejeune, North Carolina; childhood cancer	Historical reconstruction of drinking water levels using groundwater fate and transport and water-distribution system models	Maternal age and education; use of prenatal vitamins; working; smoking; alcohol use; 1st trimester fever; child's sex; paternal occupational exposure to solvents	Strengths[b]: none noted by the study author Limitations[b]: small number of cases; case information obtained from surveys; non-participation of 20% of pregnancies occurring at Camp Lejeune during the study time period; interviews conducted from 20 to 37 years after the births that likely contributed to recall errors; due to small number of cases, could not distinguish effects of one chemical independent of the others; incomplete data on gestational age at birth; possible exposure misclassification
Ruckart et al. 2015; Camp Lejeune, North Carolina; adults	Historical reconstruction of drinking water levels using groundwater fate and transport and water-distribution system models	Age at diagnosis; race; service in Vietnam	Strengths[b]: none noted by the study author Limitations[b]: findings based on a small number of cases resulting in wide confidence intervals for the estimated risk estimates; due to small numbers of cases, could not distinguish effects of one chemical independent of the others

[a]Unless otherwise noted, study strengths and limitations were noted by EPA (2011e).
[b]Study strengths and limitations were noted by the study authors.

epidemiological studies assessing the potential carcinogenicity of oral trichloroethylene, the EPA IRIS Toxicological Review for Trichloroethylene (EPA 2011e), IARC (2014), and NTP (2016) may be consulted.

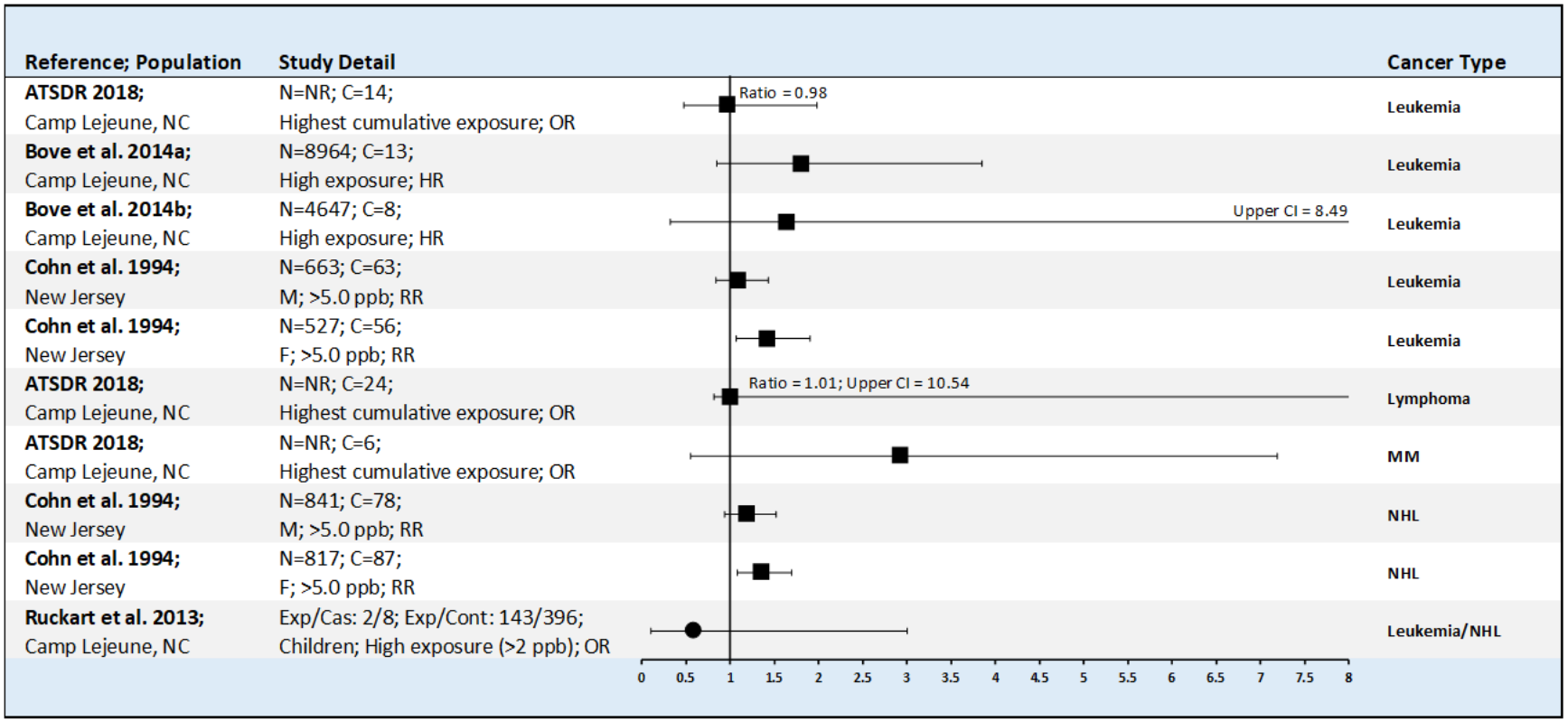
Exposure assessment methods are listed in Table 3-4. It is important to note that none of the exposure assessments included individual monitoring data or rigorous monitoring to determine individual trichloroethylene intake. Most studies provided a semi-quantitative estimate of oral exposure based on exposure and leaching models. Exposure misclassification is possible from use of these models because they do not estimate individual trichloroethylene intakes, and modeled exposure of trichloroethylene may not reflect long-term drinking water exposure concentrations or tetrachloroethylene intakes.

The potential influence of confounding factors is an important consideration in the interpretation of these epidemiological studies. As summarized in Table 3-4, consideration of confounders was not consistent across studies. The Ruckart et al. (2013) study included several confounders; however, other studies evaluated few confounders. Lack of consideration of confounding factors may add uncertainty to interpretation of study results. For assessments of the carcinogenic potential of oral trichloroethylene, it is important to consider the potential influence of exposure to other solvents and chemicals. In all studies, drinking water contained multiple contaminants. For example, drinking water at Camp Lejeune was contaminated with trichloroethylene, tetrachloroethylene, benzene, vinyl chloride, and trans-1,2-dichloroethylene (Ruckart et al. 2013). None of the studies considered co-contaminants in water as a confounding factor; therefore, it is difficult to rule out potential contributions of other chemicals. One study considered paternal occupational exposure to solvents (Ruckart et al. 2013).

Study results for hematopoietic cancers are shown in Figure 3-18; results for all other cancer endpoints are shown in Figure 3-19. These figures include information on geographic location of the population, number of participants/cases, cancer incidence, and study statistics (e.g., risk values and CIs) as reported by the study authors. Exposure classifications (e.g., qualitative or semiquantitative exposure) for presented risk values also are included. Selected studies evaluated non-Hodgkin's lymphoma, leukemia, breast cancer, and prostate cancer.

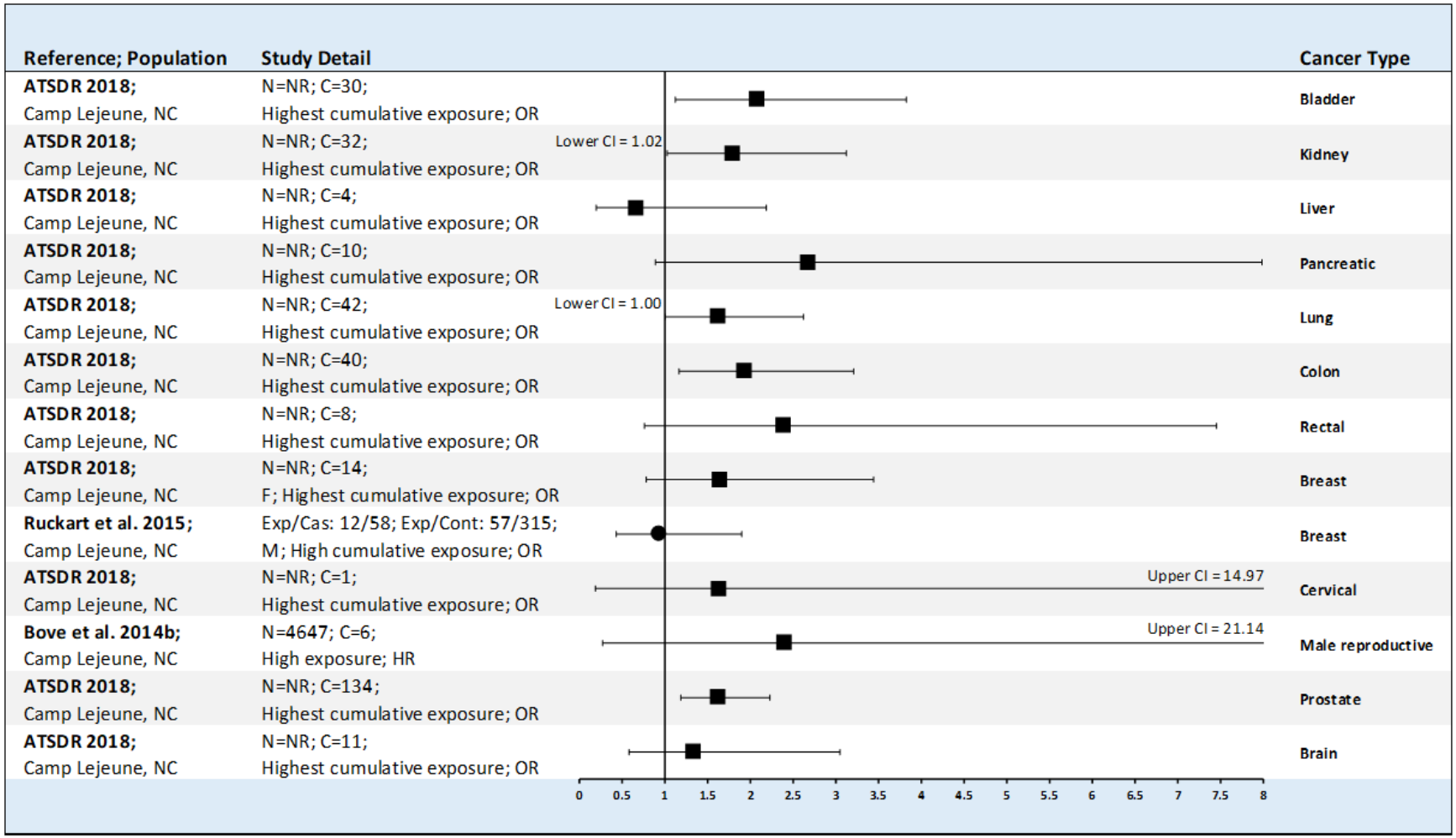
Animal Studies. Various types of cancers have been found in animals after trichloroethylene exposure by the oral route. It should be noted that the rodent bioassays employed relatively high (maximally-tolerated) chronic exposure levels. Other study design issues add to the uncertainty in interpreting the results of animal carcinogenicity studies. For example, epoxides are often used to stabilize

Figure 3-18. Summary of Epidemiological Studies Evaluating Associations between Oral Exposure to Trichloroethylene and Hematopoietic Cancers



= risk estimate and 95% CI for cohort studies; = risk estimate and 95% CI for case-control studies; C = number with specific cancer; CI = confidence interval; Exp/Cas = number of exposed cases/number of cases; Exp/Cont = number of exposed controls/number of controls; F = females; HR = hazard ratio; M = males; N = number of participants; OR = odds ratio; RR = rate ratio

Figure 3-19. Summary of Epidemiological Studies Evaluating Associations between Oral Exposure to Trichloroethylene and Other Cancers



= risk estimate and 95% CI for cohort studies; = risk estimate and 95% CI for case-control studies; C = number with specific cancer; CI = confidence interval; Exp/Cas = number of exposed cases/number of cases; Exp/Cont = number of exposed controls/number of controls; F = females; HR = hazard ratio; M = males; N = number of participants; OR = odds ratio

trichloroethylene, which degrades rapidly when exposed to light. Some epoxides are known to form reactive radicals, which may be tumor initiators themselves. In one study, B6C3F1 mice exposed by oil gavage to industrial-grade trichloroethylene (in corn oil) containing small amounts of stabilizers such as epichlorohydrin and other epoxides had significant increases in hepatocellular carcinomas in male and female mice at the low- and high-dose levels (NCI 1976). ICR/Ha Swiss mice treated by gavage with trichloroethylene-containing epoxide stabilizers had increases in forestomach tumors, which were not observed in the group receiving trichloroethylene without stabilizers (Henschler et al. 1984). The forestomach tumors were believed to be induced by the direct alkylating epoxides. Liver and lung tumors were not observed in significant numbers.

Another difficulty with some of the chronic carcinogenicity studies in animals is the poor survival rate of the rodents. No compound-related carcinogenic effects were seen in rats exposed by gavage to trichloroethylene with stabilizers in corn oil (NCI 1976), but the high mortality in all groups of rats (due to toxicity) significantly detracted from the reliability of the conclusions in this study. Survival rate also affected the evaluation of a carcinogenic response in F344 rats (NTP 1990). In this study, using epoxide-free trichloroethylene, toxic nephrosis significantly reduced survival. A small but statistically significant increase in renal tubular cell adenocarcinomas occurred in the male rats, but there was no treatment-related increase of tumors in the female rats. The findings were judged to be equivocal by the investigators. When male and female Sprague-Dawley rats were dosed by gavage with epoxide-free trichloroethylene in olive oil, there was an increase in leukemia in males but not in females (Maltoni et al. 1986). However, limitations of this study include a relatively short treatment period (52 weeks) and failure to indicate the number of surviving animals. In a study of four strains of rats, increases were found in renal tubular cell adenomas in the low-dose male Osborne-Mendel rats and in interstitial cell tumors of the testis in the high-dose Marshall rats (NTP 1988). In addition, male and female ACI and August rats showed a slight (not statistically significant) increase in proliferative tubular cell lesions. However, this study was also considered to be inadequate for evaluating carcinogenicity by the NTP Peer Review Panel because of low survival rate and conduct flaws; the test material contained an amine stabilizer at a concentration of 8 ppm, but no epichlorohydrin or 1,2-epoxybutane.

In contrast to rats, B6C3F1 mice developed hepatocellular carcinomas and hepatocellular adenomas following exposure to epoxide-free trichloroethylene (NTP 1990). The evidence that trichloroethylene is a hepatic carcinogen in mice but not rats was supported by results of a study in which rats and mice were given trichloroethylene at 500 mg/kg/day by oil gavage for up to 14 days, and then assayed for site-specific cell proliferation in various organs (Klaunig et al. 1991). Thymidine labelling of isolated

hepatocytes showed increased DNA synthesis in exposed mice but not exposed rats, while renal DNA synthesis was unchanged in both species. The human relevance of trichloroethylene-induced hepatocarcinogenicity in mice has been questioned, in part, because relatively high exposure levels were required to induce hepatocarcinogenicity in mice, trichloroethylene did not induce liver tumors in rats, mice metabolize trichloroethylene more rapidly than rats and metabolism of trichloroethylene in humans is thought to be more comparable to that of rats than mice, and a peroxisome proliferator-activated receptor alpha (PPARα) mode of action for a major trichloroethylene metabolite (trichloroacetate) that induces liver tumors in mice is of questionable relevance to humans (Corton 2008; EPA 2011e; Klaunig et al. 2003; NRC 2009; and others).

CELs from all reliable studies are recorded in Table 3-3 and plotted in Figure 3-17.

The EPA concluded that trichloroethylene is carcinogenic to humans by all routes of exposure based on convincing evidence of a causal association between trichloroethylene exposure in humans and kidney cancer (EPA 2011e). EPA calculated an adult-based oral slope factor of 4.6×10^{-2} per mg/kg/day (rounded to 5×10^{-2} per mg/kg/day) resulting from PBPK model-based route-to-route extrapolation of the inhalation unit risk estimate based on human kidney cancer risks reported by Charbotel et al. (2006) and adjusted for potential risk for tumors at multiple sites using human epidemiologic data (EPA 2011e; IRIS 2011). EPA stated that the oral slope factor for trichloroethylene should not be used with exposures exceeding 10 mg/kg/day because above this level, the route-to-route extrapolation relationship is no longer linear (EPA 2011e; IRIS 2011). EPA also stated that the oral slope factor of 4.6×10^{-2} per mg/kg/day, calculated from adult exposure data, does not reflect presumed increased early-life susceptibility to trichloroethylene-induced kidney tumors (EPA 2011e; IRIS 2011). For risk assessments based on specific exposure scenarios, EPA (2011e; IRIS 2011) recommends the application of ADAFs: 10 for <2 years of age, 3 for 2 to <16 years of age, and 1 for ≥16 years of age (EPA 2005a). Based on exposure from age 0 to 70 years with age-specific 90th percentile water consumption rates, the lower bound estimates (lower 95% confidence limits) on the drinking water concentrations associated with risk of 1×10^{-4}, 1×10^{-5}, and 1×10^{-6} are 50, 5, and 0.5 µg/L, respectively (EPA 2011e; IRIS 2011). Doses (in mg/kg/day) associated with risk of 1×10^{-4}, 1×10^{-5}, 1×10^{-6}, and 1×10^{-7} are presented in Figure 3-17.

3.2.3 Dermal Exposure

Occupational exposure to trichloroethylene may involve dermal as well as inhalation exposure routes; however, no occupational studies were located that address dermal exposures.

3.2.3.1 Death

No studies were located regarding death of humans after dermal exposure to trichloroethylene.

One group of investigators reported that the dermal LD_{50} for trichloroethylene in rabbits is >29 g/kg, but did not report any other details (Smyth et al. 1969). No other dermal lethality data studies were available.

3.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, or ocular effects in humans or animals after dermal exposure to trichloroethylene.

Hepatic Effects. Jaundice and abnormal liver function tests including increases in serum transaminase levels have been noted in individuals occupationally exposed to trichloroethylene by both dermal and inhalation exposure (Bauer and Rabens 1974; Phoon et al. 1984).

In one set of modified guinea pig maximization tests, guinea pigs were treated by intradermal injections of trichloroethylene in the induction phase followed by challenge dermal application (Tang et al. 2002, 2008). Among the guinea pigs that exhibited dermal sensitization reactions (>60% of the treated animals), mean relative liver weight was significantly increased (18% greater than controls) and serum ALT and AST levels were significantly increased (1.6- and 3.2-fold, respectively, greater than controls). Liver effects were not seen in those guinea pigs that did not exhibit evidence of trichloroethylene-induced dermal sensitization reactions. No studies were located regarding hepatic effects in animals after dermal exposure to trichloroethylene.

Renal Effects. No studies were located regarding renal effects in humans following dermal exposure to trichloroethylene.

In a modified guinea pig maximization test, 38 female guinea pigs were treated by intradermal injection of trichloroethylene followed by sensitizing dermal application at 7 days postinjection and challenge

dermal application at 14 days postinjection (Yu et al. 2012). Histopathological evidence of trichloroethylene-induced renal effects (swelling of tubular epithelial cell mitochondria, vacuolar degeneration, and atrophy of microvilli) and markedly elevated urease and urinary protein were noted in the group of trichloroethylene-sensitized animals.

Dermal Effects. Because of the high volatility of trichloroethylene, human occupational exposure by dermal routes usually includes some unspecified amount of inhalation exposure. Severe exfoliative dermatitis was reported in a man exposed to unspecified levels of 90–98% pure trichloroethylene for 3 hours in an unventilated room (Nakayama et al. 1988). A patch test using both trichloroethylene and trichloroethanol, a metabolite, yielded positive results for this man and negative results for 10 control subjects. This suggests that the patient had an allergic reaction to trichloroethylene. Skin irritations, burns, and rashes, such as generalized dermatitis, have resulted from occupational exposure to trichloroethylene (Bauer and Rabens 1974; Conde-Salazar et al. 1983; Phoon et al. 1984; Waller et al. 1994). The dermal effects are usually the consequence of direct skin contact with concentrated solutions, which results in desiccation due to the defatting action of the solvent. It is also possible that adverse dermatological conditions may also be mediated by immunological responses in some persons.

A study using skin samples from healthy humans revealed that trichloroethylene extracts lipids from the stratum corneum (Goldsmith et al. 1988). The study indicates that lipid extraction is the reason for whitened skin following exposure to organic solvents such as trichloroethylene.

Only one animal study was located. In this investigation, guinea pigs exhibited considerable erythema, edema, and increased epidermal thickness following an uncovered dermal exposure to undiluted trichloroethylene 3 times/day for 3 days (Anderson et al. 1986).

3.2.3.3 Immunological and Lymphoreticular Effects

Information regarding immunological effects in humans exposed to trichloroethylene derives mainly from occupational scenarios that involve inhalation and dermal exposure routes; refer to Section 3.2.1.3 for a discussion of immunological effects following occupational exposure to trichloroethylene.

In one set of modified guinea pig maximization tests, strong dermal sensitization reactions (erythema and edema) were elicited in guinea pigs treated by intradermal injections of trichloroethylene in the induction phase followed by challenge dermal application; dermal sensitization rates were on the order of 66–71%

(Tang et al. 2002, 2008). In another modified guinea pig maximization test in which 38 female guinea pigs were treated by intradermal injection of trichloroethylene followed by sensitizing dermal application at 7 days postinjection and challenge dermal application at 14 days postinjection, 24 animals (63%) exhibited dermal allergenic reactions (Yu et al. 2012).

3.2.3.4 Neurological Effects

In studies designed to examine dermal absorption of trichloroethylene, emersion of the hand (Sato and Nakajima 1978) or thumb (Stewart and Dodd 1964) for 30 minutes was reported to be painful. The pain was described as excruciating in one study (Sato and Nakajima 1978), and in another study, it was described as mild by one subject and moderately severe by two subjects (Stewart and Dodd 1964). Occupational exposure to trichloroethylene that involved both dermal and inhalation exposure has been reported to result in dizziness, headache, insomnia, lethargy, forgetfulness, and loss of feeling in the hands and feet (Bauer and Rabens 1974; Kohlmuller and Kochen 1994).

No studies were located regarding neurological effects in animals following dermal exposure to trichloroethylene.

3.2.3.5 Reproductive Effects

No studies were located regarding reproductive health effects in humans or animals after dermal exposure to trichloroethylene.

3.2.3.6 Developmental Effects

No studies were located regarding developmental health effects in humans or animals after dermal exposure to trichloroethylene.

3.2.3.7 Cancer

Percutaneous absorption of trichloroethylene through intact human skin is quite limited, relative to absorption following ingestion or inhalation exposure. However, dermal exposure can significantly contribute to total systemic exposure when there is prolonged or repeated contact with concentrated trichloroethylene solutions.

The combined incidence of stomach, liver, prostate, and lymphohematopoietic cancers was increased among 2,050 male and 1,924 female Finnish workers occupationally exposed primarily to trichloroethylene (Anttila et al. 1995). The workers were exposed principally by inhalation, although there was some dermal contact. The statistical power of this study was low.

Experiments were conducted in which purified trichloroethylene (1 mg in acetone) was applied to the shaved backs of female ICR/Ha Swiss mice (Van Duuren et al. 1979). In an initiation-promotion study, a single application of trichloroethylene was followed by repeated application of phorbol myristate acetate (PMA) promoter. In a second study, mice were treated with trichloroethylene 3 times/week without a promoter. No significant tumor incidences were observed in these studies. Doses used in these studies were well below the maximum tolerated dose, which is often not reached in dermal studies.

3.3 GENOTOXICITY

The potential genotoxicity of trichloroethylene has been assessed to a small extent in humans and to a much greater degree in mammalian and nonmammalian test systems. Genotoxic effects produced by tetrachloroethylene are thought to be the result of reactive metabolic intermediates of metabolism of tetrachloroethylene (Cichoki et al. 2016; EPA 2011e; IARC 2014). Results of *in vivo* and *in vitro* genotoxicity testing of trichloroethylene are summarized in Tables 3-5 and 3-6, respectively. Human data provide inconclusive evidence for the genotoxicity of trichloroethylene. Results of testing in mammalian and nonmammalian test system indicate a potential for trichloroethylene to induce chromosomal damage. The weight of evidence suggests that trichloroethylene does not act directly as a mutagenic agent, but that the observed mutagenic responses are likely due to production of mutagenic metabolites and/or the presence of mutagenic epoxide stabilizers in commercial-grade trichloroethylene. The evidence for these findings is discussed below.

A marked increase in the incidence of chromosomal abnormalities, such as gaps, breaks, translocations, deletions, inversions, and hyperdiploidy, was detected in the lymphocytes of occupationally exposed workers (Rasmussen et al. 1988). The same researchers also looked at the frequency of nondisjunction for the Y chromosome in sperm; the result was negative. One problem with this investigation is that information regarding exposure to other potentially mutagenic factors, such as x-rays, viral infections, alcohol, and workplace chemicals, was unavailable for the control group (Rasmussen et al. 1988). An increase in hypodiploid cells was detected in an earlier study of trichloroethylene exposed workers, but

Table 3-5. Genotoxicity of Trichloroethylene *In Vivo*

Species/test system	End point	Results	Reference
Drosophila melanogaster	Chromosomal aberrations	–	Beliles et al. 1980
Human (occupational exposure)	Chromosomal aberrations	+	Rasmussen et al. 1988
Mouse	Chromosomal aberrations	–	Kligerman et al. 1994
Rat	Chromosomal aberrations	–	Kligerman et al. 1994
Rat	Chromosomal aberrations	–	Sujatha and Hegde 1998
Mouse	Micronucleus formation	+/–	Duprat and Gradiski 1980
Mouse	Micronucleus formation	–	Allen et al. 1994
Mouse	Micronucleus formation	–	Kligerman et al. 1994
Rat	Micronucleus formation	–	Kligerman et al. 1994
Rat	Micronucleus formation	+	Robbiano et al. 1998; 2004
Rat	Micronucleus formation	+	Sujatha and Hegde 1998
Human (occupational exposure)	Sister chromatid exchange	(+)	Gu et al. 1981a
Human (smokers, occupational exposure)	Sister chromatid exchange	+	Seiji et al. 1990
Human (nonsmokers, occupational exposure)	Sister chromatid exchange	–	Seiji et al. 1990
Human (smokers, nonsmokers, occupational exposure)	Sister chromatid exchange	–	Nagaya et al. 1989a
Mouse	Sister chromatid exchange	+	Kligerman et al. 1994
Rat	Sister chromatid exchange	–	Kligerman et al. 1994
Rat	C-mitotic changes	+	Sujatha and Hegde 1998
Mouse (spot test)	Gene mutation	(+)	Fahrig 1977
Mouse	Dominant lethal mutation	–	Slacik-Erben et al. 1980
Mouse	DNA-protein cross-links	–	Keller and Heck 1988[a]
Human (occupational exposure)	Nondisjunction of Y chromosome in sperm	–	Rasmussen et al. 1988
Rat (DNA damage)	Single-strand breaks	(+)	Nelson and Bull 1988
Rat (DNA damage)	Single-strand breaks	–	Parchman and Magee 1982
Rat (DNA damage)	Single-strand breaks	+	Nelson and Bull 1988
Mouse (DNA damage)	Single-strand breaks	+	Walles 1986
Mouse (DNA damage)	Single-strand breaks	+	Nelson and Bull 1988
Rat (DNA damage)	Single-strand breaks	+	McLaren et al. 1994
Rat (DNA damage)	Single-strand breaks	+	Robbiano et al. 2004
Rat (hepatocyte UDS)	Unspecified DNA damage	–	Mirsalis et al. 1989
Mouse (hepatocyte UDS)	Unspecified DNA damage	–	Mirsalis et al. 1989
Mouse (hepatocyte UDS)	Unspecified DNA damage	–	Doolittle et al. 1987
Rat (hepatocyte DNA damage)	Oxidative DNA damage	+	Toraason et al. 1999

Table 3-5. Genotoxicity of Trichloroethylene *In Vivo*

Species/test system	End point	Results	Reference
Rat (comet assay)	DNA breakage	–	Clay 2008
Mouse	DNA adducts	+	Kautiainen et al. 1997
Mouse	DNA adducts	+	Mazzullo et al. 1992
Rat	DNA adducts	+	Mazzullo et al. 1992
Mouse	Protein adducts	+	Kautiainen et al. 1997
Rat	Protein adducts	+	Halmes et al. 1997
Mouse host-mediated assays:			
Schizosaccharomyces pombe	Gene mutation	–	Rossi et al. 1983
Saccharomyces cerevisiae	Gene mutation	+	Bronzetti et al. 1978

– = negative result; + = positive result; (+) = weakly positive result; +/– = inconclusive result; DNA = deoxyribonucleic acid; UDS = unscheduled DNA synthesis

Table 3-6. Genotoxicity of Trichloroethylene *In Vitro*

Species/test system	End point	Results: With activation	Results: Without activation	Reference
Prokaryotic organisms:				
Salmonella typhimurium TA98, TA100, TA1535, TA1537	Gene mutation	–	–	Mortelmans et al. 1986
S. *typhimurium* TA98, TA100	Gene mutation	–	–	Waskell 1978
S. *typhimurium* TA100	Gene mutation	–	–	Henschler et al. 1977
S. *typhimurium* TA1535	Gene mutation	–	–	Shimada et al. 1985
S. *typhimurium* TA100	Gene mutation	(+)	–	Baden et al. 1979
S. *typhimurium* TA100	Gene mutation	(+)	–	Bartsch et al. 1979
S. *typhimurium* TA100	Gene mutation	(+)	–	Crebelli et al. 1982
S. *typhimurium* TA100	Gene mutation	(+)	–	Simmon et al. 1977
S. *typhimurium* TA1535	Gene mutation	+/–	+/–	Baden et al. 1979
S. typhimurium TA98, TA100 (stabilized TCE, preincubation assay)	Gene mutation	–	–	McGregor et al. 1989
S. *typhimurium* (unstabilized TCE, vapor assay)	Gene mutation	–	No data	McGregor et al. 1989
S. *typhimurium* (stabilized TCE, vapor assay)	Gene mutation	+ (TA1535) +/– (TA100) – (TA98)	+ (TA1535) +/– (TA100) – (TA98)	McGregor et al. 1989
S. *typhimurium* YG7108pin3ERb$_5$	Gene mutation	No data	–	Emmert et al. 2006
Escherichia coli E12	Gene mutation	+/–	–	Greim et al. 1975
Eukaryotic organisms:				
Fungi:				
Saccharomyces cerevisiae D7	Gene mutation	–	–	Koch et at 1988
S. cerevisiae	Gene mutation	+	–	Bronzetti et al. 1978
Schizosaccharomyces pombe	Gene mutation	–	–	Rossi et al. 1983
Aspergillus nidulans	Gene mutation	No data	(+)	Crebelli et al. 1985
S. cerevisiae D7	Recombination	No data	+	Callen et al. 1980
S. cerevisiae D4	Recombination	No data	–	Callen et al. 1980
S. cerevisiae	Recombination	+	–	Bronzetti et al. 1978
A. nidulans	Recombination	No data	(+)	Crebelli et al. 1985
S. cerevisiae D7	Gene conversion	–	–	Koch et al. 1988
S. cerevisiae D61.M	Mitotic aneuploidy	+	+	Koch et al. 1988

Table 3-6. Genotoxicity of Trichloroethylene *In Vitro*

Species/test system	End point	Results: With activation	Results: Without activation	Reference
Mammalian cells:				
Rat primary hepatocytes (UDS)	DNA damage	No data	–	Shimada et al. 1985
Rat hepatocytes	DNA single-strand breaks	No data	+	Robbiano et al. 2004
Human hepatocytes	DNA single-strand breaks	No data	+	Robbiano et al. 2004
Human lymphocytes (UDS)	DNA damage	+/–	+/–	Perocco and Prodi 1981
Human WI-38 (UDS)	DNA damage	(+)	(+)	Beliles et al. 1980
Rat hepatocytes	Micronucleus formation	No data	+	Robbiano et al. 2004
Human hepatocytes	Micronucleus formation	No data	+	Robbiano et al. 2004
C3T3 mouse cells	Cell transformation	No data	(+)	Tu et al. 1985
Rat embryo cells	Cell transformation	No data	+	Price et al. 1978
Syrian hamster embryo cells	Cell transformation	No data	–	Amacher and Zelljadt 1983
Rat hepatocytes	Protein adducts	No data	+	Griffin et al. 1998
Human hepatocytes	Protein adducts	No data	+	Griffin et al. 1998

– = negative result; + = positive result; +/– = inconclusive result; (+) = weakly positive result;
DNA = deoxyribonucleic acid; TCE = trichloroethylene; UDS = unscheduled DNA synthesis

chromosomal breakage was not observed (Konietzko et al. 1978). Results from this study were considered inconclusive because of a lack of matched controls, the possible exposure of workers to other potentially mutagenic chemicals, and the possibility that the incidence of hypodiploid cells was the result of the chromosome preparation technique (EPA 1985c).

Cigarette smoking and trichloroethylene exposure may act synergistically to increase the rate of sister chromatid exchange (Seiji et al. 1990). Because cigarette smoking is a well-recognized factor in increased sister chromatid exchange, this study included comparisons of trichloroethylene-exposed and nonexposed individuals, who were smokers or nonsmokers. The only group with an increased frequency of sister chromatid exchange consisted of individuals who smoked and were exposed to trichloroethylene. However, this study had several limitations. The lack of an increase in unexposed smokers compared to nonsmokers may be due to the small number of smokers (n=7) or to the fact that they smoked no more than 5–10 cigarettes/day. In addition, concomitant exposure to other solvents occurred. In a similar investigation of sister chromatid exchange, negative results were obtained for both smokers and nonsmokers exposed to trichloroethylene (Nagaya et al. 1989a). As expected, the average frequency for sister chromatid exchange appeared to be higher among smokers than nonsmokers regardless of trichloroethylene exposure; unfortunately, statistical testing regarding increased sister chromatid exchange frequency among smokers was not performed. An earlier study did suggest a positive effect of trichloroethylene on increased sister chromatid exchange, but exposure to other chemicals may have confounded these results (Gu et al. 1981b).

The results from *in vivo* animal studies provide some evidence for the genotoxicity of trichloroethylene. High oral doses of trichloroethylene resulted in single-strand breaks in liver cells of B6C3F1 mice and Sprague-Dawley rats (Nelson and Bull 1988). The mice were much more sensitive to trichloroethylene than the rats. Nelson and Bull (1988) pretreated other groups of rats with small doses of trichloroethylene, phenobarbital, and ethanol (inducers of metabolism) to determine the importance of trichloroethylene metabolism in the production of single-strand breaks. Both phenobarbital and trichloroethylene pretreatments significantly increased single-strand breaks by trichloroethylene; ethanol did not. This suggests not only that trichloroethylene metabolites are important, but also that phenobarbital, not ethanol, can induce metabolic pathways involving the formation of the active metabolites of trichloroethylene. Treating the rodents with trichloroethylene metabolites (TCA, DCA, and chloral hydrate) produced strand breaks at lower doses than trichloroethylene. This implies that one or more of these metabolites is involved in strand breakage (Nelson and Bull 1988). An increase in strand breaks may reflect an effect on the DNA repair process rather than an increase in break formation.

Single-strand breaks in DNA of kidney and liver cells were observed in mice following a single intraperitoneal injection of trichloroethylene (Walles 1986). The breaks were repaired within 24 hours. It has been suggested that the single-strand breaks may be the result of repair of alkylated bases, the influence of oxygen radicals formed during the biotransformation of the substances, or the destruction of DNA by the autolysis of cells at toxic doses (Walles 1986). Oxidative DNA damage was reported in liver cells from rats administered a single intraperitoneal injection of trichloroethylene (Toraason et al. 1999). Increased incidences of micronuclei and DNA single-strand breaks were observed in kidney cells of rats given a single oral dose of trichloroethylene (Robbiano et al. 1998). Sujatha and Hegde (1998) reported increased micronucleus formation and C-mitotic changes (increased mitotic index, decreased frequencies of anaphases) in bone marrow cells from mice administered trichloroethylene intraperitoneally, but no effect on incidence of chromosomal aberrations. Covalent binding to DNA, RNA, and/or proteins from various organs in rats and mice after intraperitoneal injection has been observed (Halmes et al. 1997; Kautiainen et al. 1997; Mazzullo et al. 1992).

Other investigators found no evidence for DNA damage in trichloroethylene-treated rats or mice (Doolittle et al. 1987; Mirsalis et al. 1989; Parchman and Magee 1982). There was, however, evidence for an increased rate of DNA synthesis in mice (Doolittle et al. 1987; Mirsalis et al. 1989). Trichloroethylene gave a clearly negative response in a comet assay designed to assess whether trichloroethylene was involved in DNA breakage in the proximal tubules of rat kidneys (Clay 2008).

In a dominant lethal study, male mice were exposed to trichloroethylene concentrations ranging from 50 to 450 ppm for 24 hours and mated to unexposed females; the results were negative (Slacik-Erben et al. 1980). The splenocytes of mice exposed to up to 5,000 ppm trichloroethylene for 6 hours exhibited no aberrations in sister chromatid exchange or cell cycle progression and no increase in the number of micronuclei in cytochalasin B-blocked binucleated cells or bone marrow polynucleated erythrocytes (Kligerman et al. 1994). In the same study, however, rats under the same exposure regime showed a dose-related increase in bone marrow micronuclei, as well as a reduction in polychromatic erythrocytes at 5,000 ppm, indicating the possibility of aneuploidy. These results are contrary to those expected since mice are generally more susceptible to cellular injury and tumor induction by trichloroethylene than rats because trichloroethylene is more readily activated to reactive metabolites in mice than rats (or humans). A possible explanation is that chloral hydrate, a metabolite of trichloroethylene, is known to induce aneuploidy in the predominant pathways in rats, whereas in mice, the chloral hydrate pathway becomes saturated.

The results from *in vitro* studies do not provide strong support for the genotoxicity of trichloroethylene (Table 3-3). Assessments of trichloroethylene for mutagenic potential in various strains of *Salmonella typhimurium* have provided negative or at most weakly positive results (Baden et al. 1979; Bartsch et al. 1979; Henschler et al. 1977; McGregor et al. 1989; Mortelmans et al. 1986; Shimada et al. 1985; Waskell et al. 1978). Baden et al. (1979) reported a weakly positive result for strain TA1535 in the presence and absence of exogenous metabolic activation. Weakly positive results were reported for strain TA100 in the presence, but not the absence of exogenous metabolic activation (Baden et al. 1979; Bartsch et al. 1979; Crebelli et al. 1982; Simmon et al. 1977); the response was stronger using S-9 mix from mouse liver compared to rat liver (Simmon et al. 1977). McGregor et al. (1989) assessed whether oxirane compounds used to stabilize trichloroethylene influenced the outcome of gene mutation assays. Unstabilized trichloroethylene did not induce gene mutations in strains TA 98 or TA100 in a preincubation assay (with or without exogenous metabolic activation) or a vapor assay (with exogenous metabolic activation). Vapors of stabilized trichloroethylene induced a mutagenic response in strain TA1535 both with and without exogenous metabolic activation, an apparently weak mutagenic response in strain TA100, and no mutagenic response in strains TA98 or TA100. Assays of epoxybutane and epichlorohydrin, two common stabilizers used for trichloroethylene, resulted in positive responses in strains TA100 and TA1535 in the absence of exogenous metabolic activation. These results indicate that the mutagenic response observed for stabilized trichloroethylene is likely a response to stabilizers rather than to trichloroethylene itself. Henschler et al. (1977) found no evidence of mutagenicity in strain TA100 exposed to technical-grade trichloroethylene that included 0.22% epichlorohydrin and 0.2% epoxybutane; both epichlorohydrin and epoxybutane elicited a mutagenic response when tested separately. Trichloroethylene was not mutagenic to the *S. typhimurium* strain YG7108pin3ERb$_5$ (a strain expressing cytochrome P450) in the absence of exogenous metabolic activation (Emmert et al. 2006). Greim et al. (1975) reported a weakly positive mutagenic response in *Escherichia coli* strain E12 in the presence, but not in the absence, of exogenous metabolic activation.

The potential for epoxide-free trichloroethylene to induce gene mutations and mitotic segregation (recombination) in the fungus *Aspergillus nidulans* was assessed by Crebelli et al. (1985). No increase in mutation frequency was observed when colonies were plated onto selected media and then exposed to trichloroethylene vapors; however, a weakly positive response was elicited when colonies were grown in the presence of trichloroethylene and then plated onto selected media. Significantly increased numbers of colonies with haploids and non-disjunctional diploids (measures of mitotic segregation) were observed in trichloroethylene-exposed colonies and in colonies exposed to trichloroethanol or chloral hydrate

(trichloroethylene metabolites) compared to unexposed controls. These results indicate that trichloroethylene metabolism may have played a role in the mutagenic and mitotic segregation responses.

Significantly increased frequencies of mitotic gene conversion and recombination were observed in an assay of the D7 strain of the yeast *Saccharomyces cerevisiae* exposed to trichloroethylene, but there was no significant effect on the D4 strain that expresses 5 times lower cytochrome P450 concentration than strain D7 (Callen et al. 1980). Bronzetti et al. (1978) reported significantly increased frequencies of gene mutations and recombination in *S. cerevisiae* strain D7 in the presence, but not in the absence, of exogenous metabolic activation. Koch et al. (1988) found no significant effect of trichloroethylene on frequencies of gene mutations or recombination in *S. cerevisiae* strain D7 in the presence or absence of exogenous metabolic activation, but noted trichloroethylene-induced mitotic aneuploidy in *S. cerevisiae* strain D61.M in the presence and absence of exogenous metabolic activation.

An unscheduled DNA synthesis (UDS) assay with human lymphocytes was indeterminate for DNA damage when tested with and without exogenous metabolic activation (Perocco and Prodi 1981). An *in vitro* UDS assay with human WI-38 lung cells was only weakly positive (Beliles et al. 1980). A UDS assay for rat hepatocytes was negative for DNA damage (Shimada et al. 1985). Studies using mammalian cells *in vitro* have reported positive results for cell transformation in C3T3 cells (Tu et al. 1985) and rat embryo cells (Price et al. 1978), with negative results in a cell transformation assay in Syrian hamster embryo cells (Amacher and Zelljadt 1983). Robbiano et al. (2004) reported increased incidences of micronuclei and DNA single-strand breaks in primary cultures of rat and human kidney cells exposed to trichloroethylene. Covalent binding of trichloroethylene to proteins was observed in hepatocytes from rats and humans (Griffin et al. 1998).

The genotoxicity of selected trichloroethylene metabolites has been extensively reviewed (EPA 2011e); it was concluded that there is relatively strong evidence for the genotoxicity of chloral/chloral hydrate and some evidence for the genotoxicity of other trichloroethylene metabolites, including DCA, dichlorovinyl cysteine, and dichlorovinyl glutathione.

3.4 TOXICOKINETICS

Inhalation, oral, and dermal studies in animals and humans indicate that trichloroethylene is rapidly absorbed into the bloodstream, regardless of the route, where it is then widely distributed to its target organs, which include the liver, kidneys, and cardiovascular and nervous systems. Due to its lipophilic

nature, trichloroethylene can accumulate in fat. Metabolism occurs fairly rapidly, and resulting metabolites are responsible for much of the toxic effects of trichloroethylene. Metabolic products are excreted primarily in the urine, and unabsorbed or unmetabolized trichloroethylene is exhaled in the breath. Physiologically based pharmacokinetic (PBPK) modeling has been performed for both animal and human systems (see Section 3.4.5), and the models' predictions regarding target organ dosimetry have been accurate. However, physiological and metabolic differences between humans and other animals generally complicate extrapolation of effects from one species to another (see Section 3.5.3).

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

Absorption of trichloroethylene in humans is very rapid upon inhalation exposure. Trichloroethylene has a blood/gas partition coefficient that is comparable to some other anesthetic gases (i.e., chloroform, diethylether, and methoxyfluorene), but it is more lipophilic than these gases. As a consequence of these properties, the initial rate of uptake of inhaled trichloroethylene in humans is quite high, with the rate leveling off after a few hours of exposure (Fernandez et al. 1977). The absorbed dose is proportional to the inhaled trichloroethylene concentration, duration of exposure, and alveolar ventilation rate at a given inhaled air concentration (Astrand and Ovrum 1976). Several studies indicate that 37–64% of inhaled trichloroethylene is taken up from the lungs (Astrand and Ovrum 1976; Bartonicek 1962; Monster et al. 1976).

Absorption kinetics of trichloroethylene are often monitored by measuring levels in the blood during and after exposure. Volunteers who inhaled 100 ppm for 6 hours showed a peak blood trichloroethylene level of approximately 1 μg/L after 2 hours (Müller et al. 1974). These levels fell rapidly when exposure ceased. Trichloroethylene levels in blood and breath increased rapidly in another study after initiation of a 4-hour exposure to 100 ppm, reaching near steady-state within an hour from the start of the exposure (Sato and Nakajima 1978). Three men accidentally exposed to trichloroethylene vapors (unspecified levels) for <30 minutes were hospitalized with acute symptoms and had venous blood levels ranging from 380 to 700 μg/L 4.5 hours after exposure (Kostrzewski et al. 1993).

When rats were exposed by inhalation to 50 or 500 ppm trichloroethylene for 2 hours, trichloroethylene was readily absorbed from the lungs into the circulation (Dallas et al. 1991). Uptake exceeded 90% during the first 5 minutes in both exposure groups, but decreased rapidly over the next 30 minutes to relatively constant (near steady-state) levels of 69 and 71% for the 50- and 500-ppm groups, respectively. The total

cumulative uptakes were 8.4 mg/kg in the 50-ppm group and 73.3 mg/kg in the 500-ppm group. Percentage systemic uptake of trichloroethylene was time dependent but not concentration dependent. Levels of trichloroethylene in exhaled breath reached near steady-state soon after the beginning of exposure and were then directly proportional to the inhaled concentrations. Other inhalation studies with rats exposed to as much as 8,000 ppm seemed to follow mixed uptake kinetics, with an initial slow first-order process followed by a saturable uptake process (Andersen et al. 1980). The kinetic constant, K_m was estimated as 463 ppm and maximum velocity, V_{max} was estimated as 146 ppm/kg/hour (24.3 mg/kg/hour).

Because most of the systemic absorption of inhaled trichloroethylene and other volatile organic compounds (VOCs) occurs in the alveoli, the extent of absorption of inhaled trichloroethylene depends upon the blood:air partition coefficient, the alveolar ventilation rate, and the cardiac output. Solubility in blood is a major factor determining the trichloroethylene concentration in blood leaving the lungs during inhalation exposure, as indicated by the blood:air partition coefficient. The higher the blood:air partition coefficient, the more soluble a substance in blood compared to air, and the more it binds to lipids and proteins in the blood. The blood:air partition coefficient has been reported to be 8.1–11.7 in humans, 13.3–25.82 in rats, and 13.4–15.91 in mice (EPA 2011e), which indicates that trichloroethylene is more readily absorbed by the blood of rats and mice than humans. Mean resting alveolar ventilation rates for humans, rats, and mice were reported to be 5.0, 52.9, and 116.5 mL/minute/100 g body weight, respectively; cardiac outputs of rats and mice are approximately 6 and 10 times greater, respectively, than that of humans (Brown et al. 1997). Therefore, for equivalent airborne exposure concentrations of trichloroethylene, internal doses are substantially higher in rodents than humans.

3.4.1.2 Oral Exposure

Although no actual rates of absorption have been measured in humans, cases of poisoning following ingestion indicate that absorption of trichloroethylene across the gastrointestinal mucosa is extensive (Brüning et al. 1998; DeFalque 1961; Kleinfeld and Tabershaw 1954; Stephens 1945). In one case, a woman hospitalized in a coma after drinking an unknown amount of trichloroethylene had a measured blood level of 4,500 mg/L 18 hours after ingestion, and the half-life was 20 hours (Perbellini et al. 1991). Trichloroethylene would be expected to be readily absorbed across the gastrointestinal mucosal barrier in humans because it is a small, nonpolar, and highly lipophilic compound.

Oral absorption of trichloroethylene in animals is rapid but can be influenced by fasting and the dosing vehicle. Trichloroethylene doses of 5, 10, and 25 mg/kg in 50% aqueous polyethylene glycol 400 were

administered to nonfasted rats, and a 10-mg/kg dose was administered to rats that were fasted for 8–10 hours (D'Souza et al. 1985). Trichloroethylene was rapidly and completely absorbed in the fasted rats, with peak blood concentrations seen 6–10 minutes after dosing. In nonfasted animals, peak blood trichloroethylene concentrations occurred at the same time, but peak blood levels were 2–3 times lower than those observed in fasted animals. Absorption of the compound from the gastrointestinal tract was also extended to periods of ≤9 hours after dosing of nonfasted animals. Furthermore, systemic absorption of trichloroethylene is about three times slower when administered in corn oil than when administered in water because corn oil acts as a reservoir for lipophilic chemicals such as trichloroethylene in the gut (Withey et al. 1983). Nonetheless, absorption of up to 90% of the administered dose has been observed in rats dosed by this method (Prout et al. 1985). A study of F344 rats that were fasted for 8 hours prior to oral dosing by gavage found a rapid appearance of trichloroethylene in the blood, which peaked after 0.75 hours (Templin et al. 1995). The same investigators also dosed beagle dogs and found that blood concentrations of trichloroethylene peaked after 1 hour. Absorption kinetic studies of fasted rats dosed by lipid-emulsion gavage revealed rapid appearance of trichloroethylene in the blood (typically peaking at 15 minutes post-exposure) followed by rapid disappearance (Templin et al. 1993). Rats similarly dosed with radiolabelled trichloroethylene showed rapid serum albumin adduction which peaked at 4–8 hours, then decayed with a half-life consistent with that of albumin itself (Stevens et al. 1992). However, some of the detected radioactivity may was likely due to trichloroethylene metabolites rather than the parent compound.

3.4.1.3 Dermal Exposure

Dermal absorption of trichloroethylene occurs following exposure to the vapor as well as direct contract with the liquid. Exposure of the forearm and hand of volunteers to 1.3 mmol/L (3.18×10^4 ppm) of trichloroethylene in a dynamic exposure cylinder for 20 minutes resulted in peak concentrations of trichloroethylene in the exhaled air at about 30 minutes after the initiation of exposure (Kezic et al. 2000). The calculated average dermal penetration rate was 0.049 cm/hour for trichloroethylene vapor. Rapid dermal absorption of trichloroethylene is evident from a study in which peak blood and exhaled air concentrations occurred within 5 minutes after a human subject immersed one hand in liquid trichloroethylene for 30 minutes (Sato and Nakajima 1978). Similarly, maximum penetration rates for 1 minute exposure of the volar forearm to liquid trichloroethylene occurred within 5 minutes of the start of exposure (modeled based on the time course of trichloroethylene in expired air following dermal versus inhalation exposure) (Kezic et al. 2001). The estimated dermal flux was 430 nmol/cm^2/minute.

Studies on dermal absorption of trichloroethylene in humans, as well as animals, are complicated by the fact that exposure in these studies is usually by direct contact of the skin with the undiluted chemical. Trichloroethylene is a lipophilic solvent that defats the skin and disrupts the stratum corneum, thereby enhancing its own absorption. Thus, the rate of absorption probably increases in a nonlinear fashion with greater epidermal disruption. Although the extent of absorption through the skin may be relatively modest with normal industrial use (Sato and Nakajima 1978; Stewart and Dodd 1964), there is insufficient information to evaluate the effects of chronic, low-level exposure in humans, especially when multiple routes may be involved.

To simulate environmental exposures, studies of absorption of trichloroethylene from water and soil were performed in two to four volunteers per exposure scenario (Poet et al. 2000). The estimated dermal permeability coefficients for trichloroethylene in water for 2-hour exposures were 0.015 cm/hour for immersion of the hand (exposed area in the range of 418–581 cm^2) in 4 L of 810–1,300 mg/L of trichloroethylene solution and 0.019 cm/hour for application of a total of 80 mL of 850–1,000 mg/L trichloroethylene solution in occluded patches (exposed area of 50.2 cm^2). The estimated dermal permeability coefficients for trichloroethylene in soil for 2-hour exposures were 0.0074 cm/hour for immersion of the hand in 4 kg of the 4,000–4,200 mg/kg trichloroethylene/soil mixture and 0.0043 cm/hour for application of a total of 80 g of the 3,200–21,000 mg/kg trichloroethylene/soil mixture in occluded patches. The total amounts of trichloroethylene absorbed were estimated at 27–56 g for the hand immersion in water, 2.8–3.4 g for the water patches, 19–21 g for the hand immersion in soil, and 1.2–11 g for the soil patches. The high level for the soil patches was for the highest trichloroethylene concentration in soil.

Similar experiments with rats indicated that rat skin was significantly more permeable to trichloroethylene in water and soil than was human skin (Poet et al. 2000). Permeability coefficients for rats were estimated at 0.31 cm/hour for exposure to 5 mL of 600–1,600 mg/L solution of trichloroethylene in water for 5 hours in an occluded patch (exposed area of 2.5 cm^2), 0.086 cm/hour for exposure to 1 g of a 5,000–40,600 mg/kg mixture of trichloroethylene in soil for 3 hours in a non-occluded patch (exposed area of 8 cm^2), and 0.09 cm/hour for exposure to 5 g of a 5,300–15,600 mg/kg mixture of trichloroethylene in soil for 5 hours in an occluded patch (exposed area of 8 cm^2). Total amounts of trichloroethylene absorbed were estimated at 2.7–7.5 mg for the occluded water patches, 1.7–15 mg for the non-occluded soil patches, and 14–40 mg for the occluded soil patches, with the higher amounts corresponding to the higher exposure concentrations.

Studies of undiluted liquid trichloroethylene also reported that significant amounts of trichloroethylene can be absorbed through the skin of animals. The percutaneous trichloroethylene absorption rate in mice was reported to be 7.82 μg/minute/cm^2 when 0.5 mL of liquid trichloroethylene was applied to clipped abdominal skin for 15 minutes (Tsuruta 1978). However, this may be lower than the actual rate since all metabolites resulting from the biotransformation of trichloroethylene were not determined. In guinea pigs, the blood concentration of trichloroethylene (reflecting absorption rate) during occluded patch exposure to 1 mL liquid trichloroethylene increased rapidly, peaking at 0.5 hours (0.8 μg/mL blood), and then decreased despite continuing dermal exposure for 6 hours (0.46 μg/mL blood) (Jakobson et al. 1982). This pattern is characteristic of hydrocarbon solvents with relatively high lipid solubility and low water solubility (≤100 mg/100 μL).

Percutaneous absorption was measured in female hairless guinea pigs exposed to dilute aqueous concentrations of trichloroethylene ranging from ≈0.020 to 0.110 ppm and also to a higher concentration of 100 ppm aqueous trichloroethylene (Bogen et al. 1992). The guinea pigs were exposed over a majority of their surface area for 70 minutes. The mean permeability coefficients obtained using low (0.23 mL/cm^2/hour) versus high (0.21 mL/cm^2/hour) concentrations of trichloroethylene were not significantly different, which indicates that dermal uptake of trichloroethylene from water is linear over the concentrations studied. The guinea pig may provide a reasonable model for assessing human percutaneous absorption of trichloroethylene. If the mean permeability constants obtained in the Bogen et al. (1992) study were applied to a 70-kg human with 18,000 cm^2 of dermal surface area 80% immersed during a 20-minute bath, the estimated dermal uptake is equal to the amount of trichloroethylene present in 1 L of the water used for bathing. Thus, dermal absorption may be a significant route of human exposure to trichloroethylene from water-related sources.

Studies with male and female rats given various levels of testosterone have implicated this hormone in determining the degree of dermal penetration of trichloroethylene (McCormick and Abdel-Rahman 1991). Dermal uptake of trichloroethylene in control female rats was twice that of control male rats. Male rats deprived of testosterone exhibited dermal uptake similar to that of control female rats; administration of testosterone to female rats resulted in dermal uptake similar to that of control male rats. The mechanism behind this effect is unclear.

3.4.2 Distribution

Trichloroethylene readily crosses biological membranes, resulting in rapid distribution to tissues regardless of route of exposure (EPA 2011e; NRC 2006). Route of exposure may result in greater initial distribution to portal-of-entry and first-pass organs, and higher distribution of trichloroethylene and its metabolites has been noted to organs involved in metabolism and excretion (liver, kidney, lung). Another important factor in determining distribution is the solubility of trichloroethylene in each organ, as indicated by the partition coefficient (EPA 2011e). In humans, the organ having the highest tissue:blood partition coefficient is fat (63.8–70.2) and the organ having the lowest is lung (0.48–1.7). Although adipose tissue also has the highest partition coefficient in rodents, it is smaller (22.7–36.1 in rats and 36.4 in mice) than in humans, indicating lower potential for storage of trichloroethylene in rodent fat than in human fat. A compilation of partition coefficients in these three species is available (EPA 2011e). Tissue:blood partition coefficients for brain were 2.62 for humans and 0.71–1.29 for rats; for liver were 3.6–5.9 for humans and 1.03–2.43 for rats; and for kidney were 1.3–1.8 for humans, 1.0–1.55 for rats, and 2.1 for mice.

3.4.2.1 Inhalation Exposure

Several studies of tissue distribution in humans after inhalation exposure to trichloroethylene report levels in the blood (Astrand and Ovrum 1976; Monster et al. 1976; Müller et al. 1974). In these studies, volunteers were exposed to trichloroethylene at concentrations in the range of 75–150 ppm for periods of 30 minutes to 6 hours. Once in the bloodstream, trichloroethylene is transported rapidly to various tissues, where most of it will be metabolized. Trichloroethylene was detected in the blood of neonates after the mothers had received trichloroethylene anesthesia (Laham 1970), and detectable levels (concentrations not reported) have been found in the breast milk of mothers living in urban areas (Pellizzari et al. 1982). Postmortem analyses of human tissue from persons with unspecified exposure revealed detectable levels of trichloroethylene (<1–32 μg/kg wet tissue) in most organs (McConnell et al. 1975). The relative proportions varied among individuals, but the major sites of distribution appeared to be body fat and the liver. Higher tissue concentrations of trichloroethylene were found in accidental occupational inhalation fatalities (12, 21, and 72 mg/kg in kidney, lung, and liver; 40–84 mg/L in blood [Coopman et al. 2003]; 174 mg/L in blood and 809 mg/kg in brain [Ford et al. 1995]).

In mice, the compound is cleared from the blood within 1 hour of a 100-mg/kg gavage dose (Templin et al. 1993), although binding to proteins such as hemoglobin or albumin likely influences the circulation time of trichloroethylene and its metabolites (Stevens et al. 1992). Blain et al. (1992) suggest that such

binding of trichloroethanol may allow distant structures like the visual cortex to be exposed, resulting in the changes in visual evoked potentials that they observed in rabbits inhaling trichloroethylene. Limited data also suggest that trichloroethylene can accumulate in fat following inhalation exposure in animals. There were relatively high levels of trichloroethylene in the perirenal fat (0.23 nmol/g) and the blood (0.35 nmol/g) of rats 17 hours after a 6-hour/day, 4-day exposure to 200 ppm, but virtually no trichloroethylene was found in the other tissues examined (Savolainen et al. 1977). Additional inhalation studies in mice and rats were performed to provide time course tissue distribution data for use in the development and validation of PBPK models (Greenberg et al. 1999; Keys et al. 2003; Simmons et al. 2002).

Placental transfer of trichloroethylene occurs in animals. Trichloroethylene inhaled by pregnant sheep and goats, at levels used to induce analgesia and anesthesia, is rapidly distributed into the fetal circulation, with peak levels occurring approximately 40–50 minutes after maternal exposure (Helliwell and Hutton 1950). The concentration of trichloroethylene in umbilical vein blood was comparable to that found in the maternal carotid artery.

3.4.2.2 Oral Exposure

The distribution of trichloroethylene in humans after oral exposure is poorly characterized. Case studies of oral exposure have found measurable levels in the blood (Perbellini et al. 1991; Yoshida et al. 1996) and 9.25, 78.3, and 747 μg/g in lung, kidney, and liver, and 210 μg/mL in blood (De Baere et al. 1997).

Limited data on tissue distribution following oral exposure in animals indicate that trichloroethylene is metabolized in the liver, although a portion of an absorbed dose may exceed the capacity of the liver to metabolize it during the initial pass through the liver. Trichloroethylene and its breakdown products that leave or bypass the liver are taken up by other tissues to some extent, particularly fat (Pfaffenberger et al. 1980). Rats were dosed by gavage with 1 or 10 mg trichloroethylene/rat/day for 25 days, and blood serum and adipose tissue levels of trichloroethylene and one of its breakdown products (chloroform) were determined at nine intervals during the exposure period and twice after cessation of dosing. Blood serum trichloroethylene levels were not detectable (i.e., <5 ng/mL serum) during the dosing period. Adipose tissue levels during the 25-day exposure averaged 280 and 20,000 ng trichloroethylene/g hexane-extractable fat for the 1- and 10-mg/rat/day groups, respectively. Average serum levels of chloroform (a metabolite of trichloroethylene) during the 25-day treatment period were 1,600 and 9,300 ng/mL, respectively, and average chloroform levels in fat were 100 and 480 ng/g fat, respectively. At 3–6 days

following cessation of trichloroethylene exposures, trichloroethylene and chloroform were rapidly eliminated from the fat; trichloroethylene was detected at only 1 ng/g fat at both dose levels and chloroform measured 6 ng/g fat at the low dose (1 mg/day) and was not detected at the high dose (10 mg/day). Additional studies were performed in rats and mice to provide time course tissue distribution data for use in the development and validation of PBPK models (Abbas and Fisher 1997; Keys et al. 2003).

3.4.2.3 Dermal Exposure

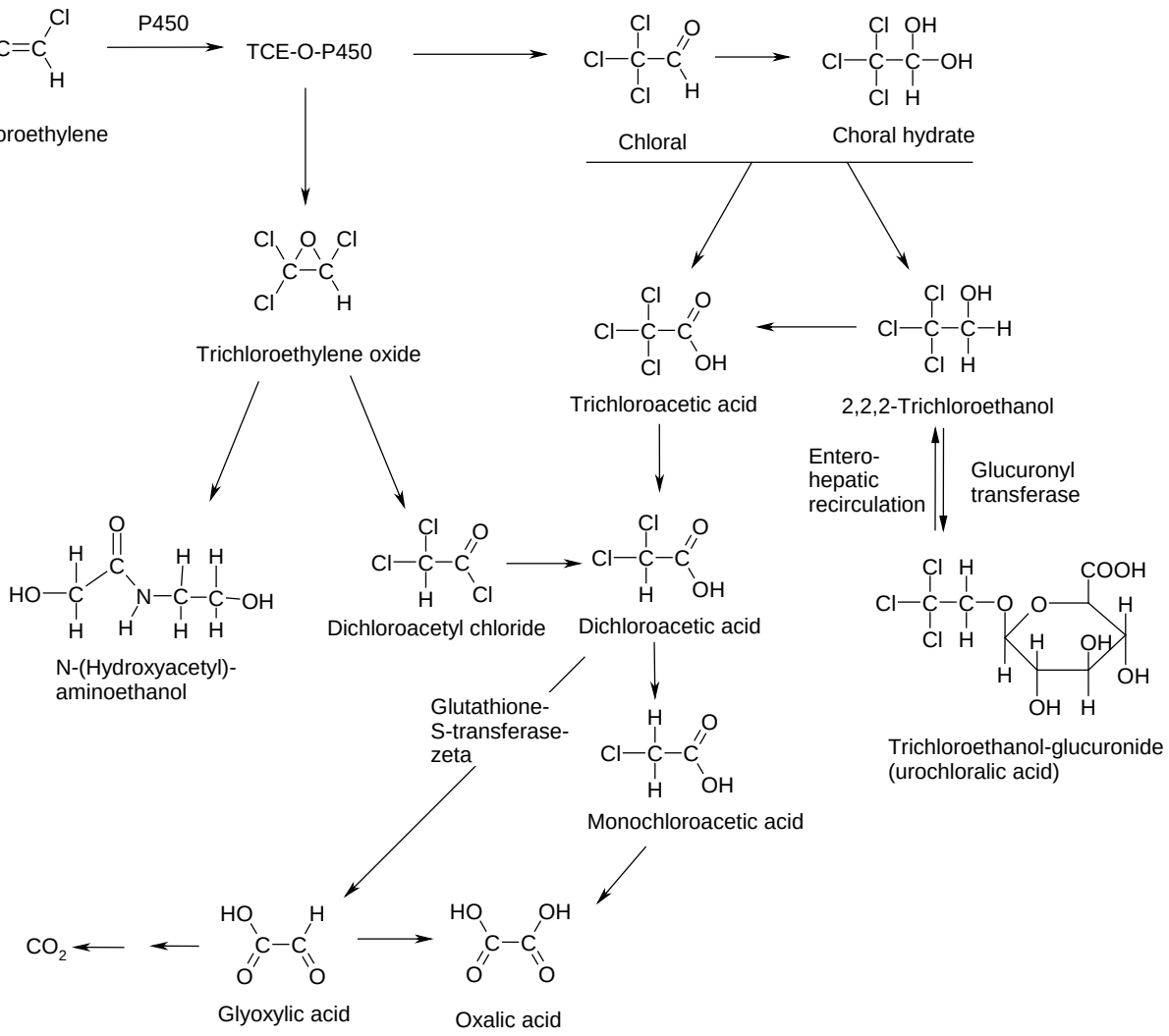
Following dermal exposure, trichloroethylene has been detected in blood and expired breath in human studies (Sato and Nakajima 1978). Studies of distribution among other tissues after dermal exposure in humans and animals were not located in the available literature.

3.4.3 Metabolism

Inhaled doses of trichloroethylene are metabolized extensively in humans. The percentage of the dose metabolized has been reported to be between 40 and 75% of the retained dose following single or repeated exposure to trichloroethylene vapors for periods of 3–8 hours at concentrations generally ranging from 50 to 350 ppm (Bartonicek 1962; Ertle et al. 1972; Fernandez et al. 1977; Kimmerle and Eben 1973a; Monster et al. 1976, 1979; Müller et al. 1972, 1974, 1975; Nomiyama and Nomiyama 1971, 1974a, 1974b, 1977; Ogata et al. 1971; Sato et al. 1977; Soucek and Vlachova 1960; Vesterberg and Astrand 1976). None of these studies provided evidence of saturation of trichloroethylene metabolism in humans, although there is some evidence of saturation of the oxidative pathway in experimental animals. The data of Nomiyama and Nomiyama (1977) and of Ikeda (1977) indicated that the liver's capacity for metabolizing inhaled doses of trichloroethylene is nonsaturable, at least for 3-hour exposures to trichloroethylene vapor at concentrations of up to 315 ppm. These investigators have suggested that at these relatively low concentrations of inhaled trichloroethylene, the parent compound was completely removed from the blood after a single pass through the liver. Saturation of trichloroethylene metabolism in humans has, however, been predicted by mathematical simulation models to occur at the relatively high exposure concentrations used in the past for anesthesia (i.e., 2,000 ppm) (Feingold and Holaday 1977).

Trichloroethylene metabolism in humans and animals occurs by cytochrome P450-dependent oxidation and glutathione (GSH)-dependent conjugation pathways (Figures 3-20 and 3-21, respectively). The major urinary metabolites of trichloroethylene in humans are the oxidative metabolites trichloroethanol,

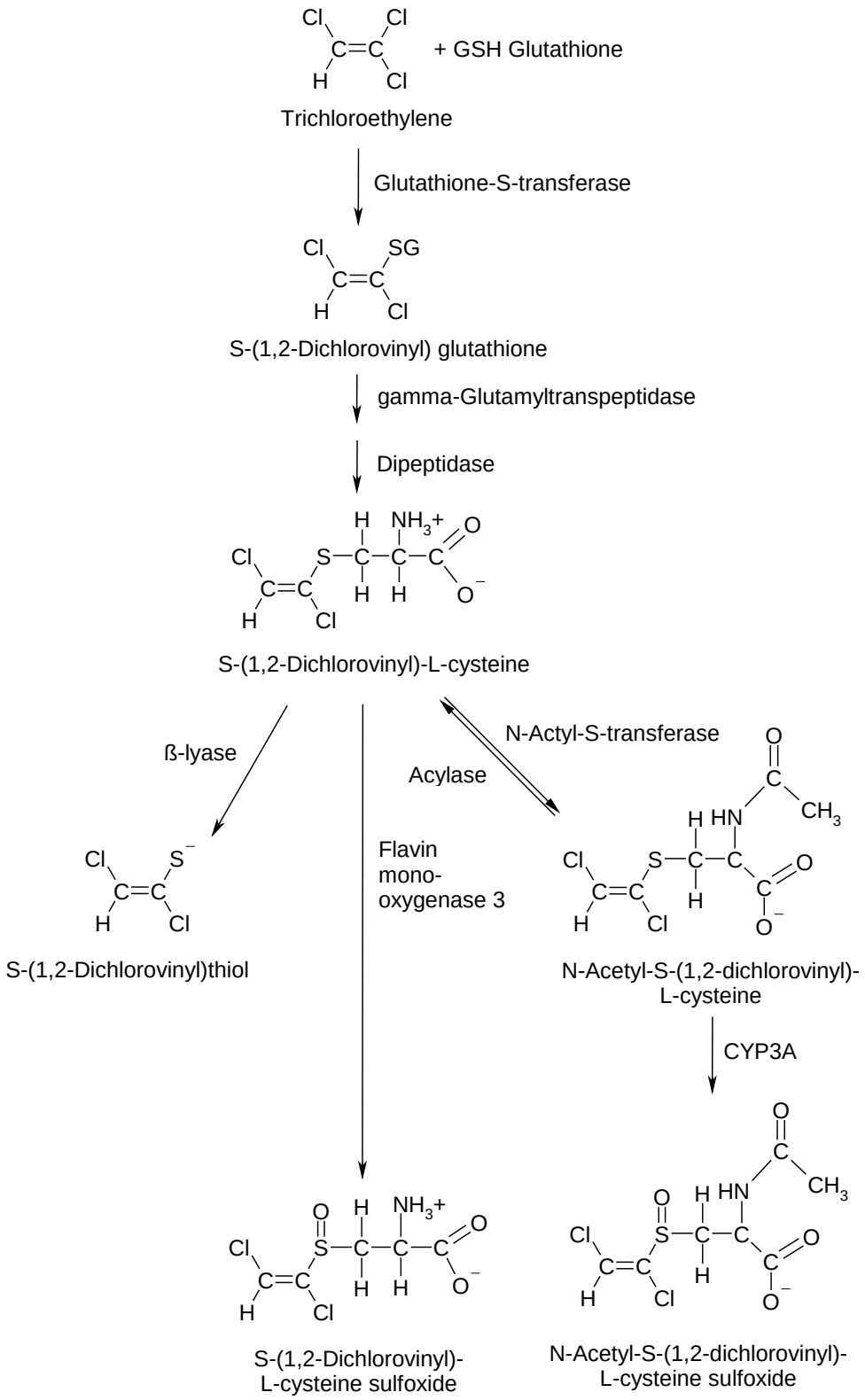
Figure 3-20. Cytochrome P450 Dependent Metabolism of Trichloroethylene



TCE-O-P450 = oxygenated trichloroethylene-P450 intermediate

Sources: EPA 2011e; Forkert et al. 2005; Lash et al. 2000a; NRC 2006; Tong et al. 1998

Figure 3-21. Glutathione Proposed Metabolism of Trichloroethylene



Sources: Bernauer et al. 1996; Chiu et al. 2006; EPA 2011e; Lash et al. 2000a, 2006; NRC 2006

trichloroethanol-glucuronide ("urochloralic acid"), and TCA (Butler 1949; Cole et al. 1975; Fisher et al. 1998; Müller et al. 1974, 1975; Nomiyama and Nomiyama 1971). Urinary trichloroethanol appears rapidly after exposure and is short lived (Skender et al. 1991; Ulander et al. 1992), whereas urinary TCA is slower to appear and is longer lived (Kostrzewski et al. 1993; Skender et al. 1991). Minor urinary metabolites in trichloroethylene-exposed humans are monochloroacetic acid (Soucek and Vlachova 1960) and N-(hydroxyacetyl)-aminoethanol (Dekant et al. 1984). Although DCA has not been reported in human urine, it has been detected in the urine of rats and in the blood of humans exposed to trichloroethylene (Fisher et al. 1998). Additional minor urinary metabolites are mercapturic acid conjugates, relatively stable metabolites resulting from the GSH-dependent metabolism of trichloroethylene (Bernauer et al. 1996; Birner et al. 1993).

The proposed cytochrome P450-dependent oxidative pathways of trichloroethylene metabolism are shown in Figure 3-20. According to the proposed metabolic scheme, trichloroethylene is oxidized by cytochrome P450 to transient intermediates: an oxygenated trichloroethylene-P450 intermediate and trichloroethylene oxide (an epoxide), which has been detected in phenobarbital-pretreated rat liver microsomes (Guengerich et al. 1991; Miller and Guengerich 1982, 1983). The oxygenated trichloroethylene-P450 intermediate results in the formation of chloral, which in the presence of water equilibrates with chloral hydrate. Chloral hydrate undergoes oxidation to TCA (Butler 1949). Alternatively, chloral hydrate can be reduced to trichloroethanol, which undergoes Phase II glucuronidation to produce trichloroethanol-glucuronide (Miller and Guengerich 1983). The oxygenated trichloroethylene-P450 intermediate also can generate trichloroethylene oxide, resulting in the formation of dichloroacetyl chloride, which rearranges to DCA (Cai and Guengerich 2000; Miller and Guengerich 1982). DCA also may be formed from the dechlorination of TCA and oxidation of trichloroethanol (Lash et al. 2000a). DCA can be further metabolized to monochloroacetic acid or glyoxylic acid, resulting in the formation of oxalic acid and CO_2 (Dekant et al. 1984; Green and Prout 1985; Lash et al. 2000a; Saghir and Schultz 2002; Tong et al. 1998).

Quantification of the amount of DCA formed is difficult because the use of strong acids in the analytical procedures can produce *ex vivo* conversion of TCA to DCA in blood, thus potentially resulting in an artifactual augmentation of DCA levels (EPA 2011e; Ketcha et al. 1996; Templin et al. 1995). The rapid metabolism of DCA at low exposure levels *in vivo* (Saghir and Schultz 2002) poses another difficulty in assessing DCA formation. Nevertheless, DCA is known to be formed from trichloroethylene oxide in aqueous systems (Cai and Guengerich 1999), and has been detected in the serum of mice orally dosed

with trichloroethylene using a method that confirmed the absence of artifactual formation of DCA from TCA during sample preparation and analysis (Kim et al. 2009a, 2009b).

Some controversy also exists regarding the role of the epoxide intermediate in trichloroethylene metabolism and toxicity. Bonse and Henschler (1976) presented theoretical considerations, based on the report of Bonse et al. (1975), suggesting that trichloroethylene is first metabolized to trichloroethylene-epoxide, which, in the presence of Lewis acids, can be rearranged to chloral *in vitro*. Since chloral is the first metabolite of trichloroethylene *in vivo*, the findings of Bonse et al. (1975) seem to support the notion that the epoxide is the intermediate between trichloroethylene and chloral. Further support for the data of Bonse et al. (1975) was provided by Uehleke et al. (1977), who showed that trichloroethylene-epoxide is formed during *in vitro* metabolism of trichloroethylene by rabbit liver microsomes and reduced nicotinamide adenine dinucleotide (NADH). However, in experiments with rat and mouse microsomes and reconstituted cytochrome P450 systems, evidence suggested the existence of a pre-epoxide transition state that involves the binding of trichloroethylene to the activated oxygen of cytochrome P450, leading to chloral formation (Miller and Guengerich 1982, 1983). The NRC (2006) and the EPA (2011e) have concluded based on this and other evidence that oxidative metabolism of trichloroethylene includes the formation of an oxygenated trichloroethylene-P450 complex as well as the epoxide as transient intermediates.

Regardless of route of exposure, and in both humans and animals, the majority of oxidative metabolism of trichloroethylene occurs in the liver (EPA 2011e; NRC 2006). The cytochrome P450-dependent metabolism of trichloroethylene was studied in hepatic microsomal fractions from 23 different humans (Lipscomb et al. 1997). As had been reported previously (Guengerich et al. 1991), CYP2E1 was the predominant form of cytochrome P450 responsible for the metabolism of trichloroethylene in human hepatic microsomes (Lipscomb et al. 1997). Incubations of trichloroethylene with the microsomal preparations resulted in hyperbolic plots consistent with Michaelis-Menten kinetics. The K_m values ranged from 12 to 55.7 μM, and were not normally distributed, and the V_{max} values range from 490 to 3,455 pmol/minute/mg protein and were normally distributed. The study authors concluded that the human variability in metabolism of trichloroethylene via cytochrome P450-dependent pathways was within a 10-fold range. CYP2E1 also is the predominant form of cytochrome P450 responsible for the metabolism of trichloroethylene in animal hepatic microsomes (Nakajima et al. 1992a). Additional cytochrome P450 isoforms identified as having a role in the oxidative metabolism of trichloroethylene are CYP1A1/2 and CYP2C11/6 (Nakajima et al. 1992a, 1993; Lipscomb et al. 1997), CYP2F and CYP2B1 (Forkert et al. 2005, 2006), and CYP3A4 (Lipscomb et al. 1997). The overall contribution of these other

cytochrome P450 isoforms is thought to be small, although CYP2F may be important in bioactivation of trichloroethylene in Clara cells in the mouse lung (Forkert et al. 2006). In addition, although trichloroethylene oxidation is decreased in CYP2E1-knockout mice exposed via inhalation, these knockout mice still had substantial capacity for trichloroethylene oxidation (Kim and Ghanayem 2006).

Experiments demonstrate that oral absorption of trichloroethylene in animals is extensive and metabolism is rapid. A study of F344 rats that were fasted for 8 hours prior to oral dosing by gavage found a rapid appearance of trichloroethylene in the blood, which peaked after 0.75 hours, while the peak concentrations of the metabolites trichloroethanol and TCA occurred at 2.5 and 12 hours, respectively (Templin et al. 1995). The same investigators also dosed beagle dogs and found that blood concentrations of trichloroethylene, trichloroethanol, and TCA peaked after 1, 2.5, and 24 hours, respectively. In both species, TCA concentration did not peak until well after the trichloroethylene concentration in blood was below detectable levels (Templin et al. 1995).

Data in animals also show that the major urinary metabolites of trichloroethylene are the relatively stable oxidative metabolites TCA, trichloroethanol, and conjugated trichloroethanol. These account for approximately 90% of the total urinary metabolites in rats (Dekant et al. 1984). Minor urinary metabolites in the rat are oxalic acid, DCA, and N-(hydroxyacetyl)-aminoethanol. Other minor urinary metabolites are mercapturic acid conjugates, relative stable metabolites resulting from the GSH-dependent metabolism of trichloroethylene (Bernauer et al. 1996; Commandeur and Vermeulen 1990; Dekant et al. 1990; Green et al. 1997). GSH conjugation, although quantitatively minor in trichloroethylene metabolism, may play an important role in the carcinogenicity/toxicity of trichloroethylene (see Section 3.5). Although specific steps involved in the formation of N-(hydroxyacetyl)-aminoethanol are unknown, one suggestion involves reaction of trichloroethylene-derived oxidative intermediates with either ethanolamine itself or with phosphatidylethanolamine (a major constituent of membranes) and subsequent metabolic breakdown of the alkylated lipids (Dekant et al. 1984); another possibility is nucleophilic attack of an endocyclic amino group of the heme moiety in cytochrome P450, resulting in inactivation of the microsomal monoxygenase system following oxidation of the trichloroethylene molecule (Dekant et al. 1984).

Phenobarbital, an inducer of some forms of cytochrome P450 (e.g., CYP2E1, CYP2B6, CYP2C9, CYP2C19), has been shown to stimulate binding and metabolism of trichloroethylene by cytochrome P450 enzymes in rat liver microsome preparations (Costa et al. 1980). Similar stimulation of cytochrome P450-mediated trichloroethylene metabolism by phenobarbital has been demonstrated *in vivo* (Carlson

1974; Moslen et al. 1977). CYP2E1 is the most prominent isozyme involved in metabolizing trichloroethylene to chloral hydrate in rat liver and human liver microsomes (Forkert et al. 2005; Guengerich and Shimada 1991; Guengerich et al. 1991; Nakajima et al. 1992a). The induction of CYP2E1 was demonstrated to be affected by the age and pregnancy status of the rat from which the microsomes were obtained (Nakajima et al. 1992b). Pregnancy decreased the metabolism of trichloroethylene, and CYP2E1 levels were lower in mature rats relative to immature rats. At puberty, the level of CYP2E1 was higher in female than in male rats. In addition, the prevalence of some isozymes was found to be greater in mice than in rats, and this difference may account for the greater capacity of mice to metabolize trichloroethylene (Nakajima et al. 1993).

Saturation of trichloroethylene metabolism in mice occurs at higher dose levels than in rats (Dallas et al. 1991; Dekant et al. 1986b; Filser and Bolt 1979; Prout et al. 1985). Male mice can metabolize inhaled trichloroethylene to a greater extent than male rats (Stott et al. 1982). In this study, virtually 100% of the net trichloroethylene uptake by mice was metabolized at both 10- and 600-ppm exposure concentrations (6-hour exposure), and there was no evidence of metabolic saturation. In rats, however, 98% of the net trichloroethylene uptake from the 10-ppm exposure was metabolized, but only 79% was metabolized at the 600-ppm exposure level. This suggested an incremental approach to the saturation of metabolism in this exposure range in the rat. Rats exposed by inhalation to trichloroethylene concentrations of 50 or 500 ppm for 2 hours showed metabolic saturation at 500 ppm (Dallas et al. 1991). This was indicated by the fact that the trichloroethylene blood levels of the 500-ppm animals progressively increased over the 2-hour period, rather than approaching equilibrium after 25 minutes, as was the case at 50 ppm.

Differential saturation of trichloroethylene metabolism by rats and mice has also been demonstrated using oral exposure regimens (Buben and O'Flaherty 1985; Prout et al. 1985). Trichloroethylene metabolism approached saturation at a dose of approximately 1,000 mg/kg for rats, whereas metabolism of trichloroethylene was still linear up to a dose of 2,000 mg/kg for mice (Prout et al. 1985). At gavage doses of trichloroethylene ≥200 mg/kg, male mice metabolized trichloroethylene at a faster rate than male rats (Larson and Bull 1992a; Prout et al. 1985); it was noted that the residence time of trichloroethylene and its metabolites was longer in rats than mice. Based on the observations of faster metabolism in mice and longer residence time in rats, the net metabolism of trichloroethylene to TCA and trichloroethanol was similar in rats and mice given single gavage doses of 1.5–23 mmol/kg (197–3,022 mg/kg) (Larson and Bull 1992a). It was also noted that the initial rates of metabolism of trichloroethylene to trichloroethanol were much higher in mice than rats, especially as the trichloroethylene dose increased, leading to greater concentrations of TCA and DCA in the blood of mice (Larson and Bull 1992a). The

greater peak blood concentrations of the metabolites TCA and DCA in mice may play an important role in the induction of hepatic tumors in mice by trichloroethylene (Larson and Bull 1992a). This has been further validated by studies in which trichloroethylene metabolites such as DCA, TCA, chloral hydrate, or 2-chloroacetaldehyde caused liver tumors in mice (Bull et al. 1993; Daniel et al. 1992; DeAngelo et al. 1991).

Although the liver is the main site of trichloroethylene metabolism in animals, there is evidence for extrahepatic trichloroethylene metabolism (Bruckner et al. 1989). After exposure to radioactive trichloroethylene vapor over an 8-hour monitoring period, Bergman (1983a) noted a continuing accumulation of trichloroethylene metabolites in the liver, kidney, and bronchi, organs in which trichloroethylene has been found to produce tumors. Further evidence for extrahepatic metabolism of trichloroethylene was presented by Hobara et al. (1986), who used a hepatic bypass procedure in dogs to demonstrate that extrahepatic metabolism of trichloroethylene accounted for 25% of the total metabolism of the chemical. Oxidation of trichloroethylene to chloral has been demonstrated in microsomal fractions from lung of rodents (Green et al. 1997; Odum et al. 1992) and from kidney of rodents and humans (Cummings et al. 2001). *In vitro* and *in vivo* data suggest that the cytochrome P450 in Type II alveolar and Clara cells of the lung is very active in metabolizing trichloroethylene, which may in turn result in pulmonary cytotoxicity and carcinogenicity (Forkert et al. 1985; Miller and Guengerich 1983; Nichols et al. 1992; Villaschi et al. 1991). As reviewed by Green (2000), the ability of the human lung to metabolize trichloroethylene is approximately 600-fold less than that of the mouse; this difference has been attributed to differences in number and morphology of Clara cells as well as species-specific differences in metabolic capacity. Clara cells have been implicated in the development of adenocarcinoma, the most frequent form of lung cancer in humans, although the role of Clara cells in lung tumorigenesis in mouse models is somewhat controversial (Reynolds and Malkinson 2010). Pulmonary cytochrome P450 isoforms important in metabolizing trichloroethylene in the Clara cells were CYP2E1 and CYP2F (Forkert et al. 2005, 2006). Results of assays using isolated rabbit pulmonary cells (Clara, Type II, and alveolar macrophages) indicate that some type of non-P450-mediated bioactivation of trichloroethylene is involved in cytotoxicity because addition of 1-aminobenzotriazole (a suicide substrate inhibitor of cytochrome P450) is not necessary to cause cytotoxicity because it failed to decrease the non-selective cytotoxicity of trichloroethylene in all three cell types (Nichols et al. 1992). Trichloroethylene metabolism also appears to be important in trichloroethylene-induced nephrotoxicity, although it appears that the principal nephrotoxic metabolites are produced via the GSH-dependent pathway, which includes the liver and kidney (Dekant et al. 1986a; Elfarra and Anders 1984).

The GSH-dependent pathway of trichloroethylene metabolism in humans and animals is outlined in Figure 3-20. Although the GSH conjugation of many compounds is associated with detoxification, trichloroethylene is bioactivated through the formation of reactive species downstream from the initial GSH conjugation; this process is thought to result in cytotoxic and carcinogenic effects, particularly in the kidney (EPA 2011e; Lash et al. 2000b; NRC 2006, 2009). The conjugation of trichloroethylene with GSH produces S-dichlorovinyl-glutathione isomers (DCVG, collectively). These isomers are S-(1,2-dichlorovinyl)glutathione (1,2-DCVG) (EPA 2011e; Lash et al. 2000a, 2000b, 2006; NRC 2006) and S-(2,2-dichlorovinyl)glutathione (2,2-DCVG) (Bernauer et al. 1996; Commandeur and Vermeulen 1990; EPA 2011e). 1,2-DCVG has been identified as a product of trichloroethylene metabolism in rat liver microsomes incubated with GSH (Dekant et al. 1990) and in isolated human and rat liver and kidney cells (Cummings and Lash 2000; Lash et al. 1995, 1999a). Following in vivo exposure to trichloroethylene, 1,2-DCVG was detected in human blood (Lash et al. 1999b) and in rat serum, blood, bile, liver, and kidney (Dekant et al. 1990; Kim et al. 2009a; Lash et al. 2006). The evidence for the 2,2-DCVG isomer is less clear and may include theoretical considerations and the identification of both 1,2- and 2,2-dichloro- downstream metabolites (Bernauer et al. 1996; Commandeur and Vermeulen 1990). Figure 3-21 shows the 1,2-dichloro- metabolites, but applies to the 2,2-dichloro- metabolites as well.

The enzymes that mediate the conjugation of trichloroethylene with GSH, glutathione S-transferases, are present in various tissues, including renal tissues, but total amounts are highest in the liver, leading to the assumption that the majority of DCVG is produced in the liver (Lash et al. 2000a, 2000b; Luo et al. 2018). Conjugation of trichloroethylene with GSH to form 1,2-DCVG was demonstrated in hepatic and renal subcellular fractions from humans, rats, and mice (Lash and Anders 1989; Lash et al. 1998, 1999a) and in isolated hepatocytes, renal cortical cells, and renal proximal tubule cells from rats (Lash and Anders 1989; Lash et al. 1998).

DCVG formed in the liver can be transported to serum and bile, taken up by the renal brush border, and metabolized to the corresponding S-dichlorovinylcysteine isomers (collectively DCVC). Metabolism of DCVG to S-(1,2-dichlorovinyl)cysteine (1,2-DCVC) or S-(2,2-dichlorovinyl)cysteine (2,2-DCVC) occurs as a two-step process by γ-glutamyl transpeptidase and dipeptidases (Elfarra and Anders 1984; Goeptar et al. 1995; Lash et al. 1988). The activities of these enzymes (measured with an alternative substrate) are much higher in the kidney than in the liver of humans, rats, and mice (EPA 2011e; Lash et al. 1998). *In vitro* rates of DCVG formation were about 8 and 13 times greater in rat and mouse liver cytosol,

respectively, than human liver cytosol (Green et al. 1997). Conversion of DCVG to DCVC also can occur in the bile or gut (EPA 2011e).

DCVC is further metabolized by N-acetyl transferases (detoxification step) to N-acetyl-S-dichlorovinyl-L-cysteine isomers (collectively NAcDCVC) in the liver or kidney (Birner et al. 1997; Duffel and Jakoby 1982). The NAcDCVC isomers, which are mercapturic acid conjugates, are N-acetyl-S-(1,2-dichloro-vinyl)-L-cysteine (NAc-1,2-DCVC) and N-acetyl-S-(2,2-dichlorovinyl)-L-cysteine (NAc-2,2-DCVC). These mercapturic acid conjugates may be released into the blood and translocated to the kidney, where they may undergo deacetylation (Wolfgang et al. 1989; Zhang and Stevens 1989) or be excreted into the urine (Bernauer et al.1996; Birner et al. 1993; Commandeur and Vermeulen 1990). Following inhalation exposure to trichloroethylene, humans excreted approximately equal concentrations of the two NAcDCVC isomers in the urine, whereas rats excreted a 3–4-fold higher concentration of NAc-2,2-DCVC than NAc-1,2-DCVC in the urine (Bernauer et al. 1996).

Alternatively, DCVC may be bioactivated by β-lyases to S-(1,2-dichlorovinyl)thiol, a transient intermediate that rearranges to reactive alkylating metabolites (Dekant et al. 1988; Goepter et al. 1995). The potential formation or fate of S-(2,2-dichlorovinyl) thiol was not mentioned in the available literature. *In vitro* studies with rat, mouse, and human kidney fractions indicated that flux through the N-acetyl transferase pathways was much higher than through β-lyase pathways; overall, the metabolic clearance through the β-lyase pathway was 11-fold greater in the rat than the human kidney (Green et al. 1997). Evidence of β-lyase activity has been reported in extrarenal tissues, such as rat and human liver and rat brain, and in intestinal microflora (EPA 2011e).

An additional bioactivating pathway involves the sulfoxidation of DCVC by flavin mono-oxygenase 3 (FMO3) and of its mercapturic acid conjugates by CYP3A. Sulfoxidation of DCVC by FMO3 was observed in microsomes from rabbit liver (Ripp et al. 1997) and human liver (Krause et al. 2003). Sulfoxidation of DCVC was not detected in microsomes from human kidney, but FMO3 expression was lower in renal than in hepatic microsomes (Krause et al. 2003). Sulfoxidation of NAc-1,2-DCVC and NAc-2,2-DCVC was catalyzed by CYP3A in microsomes from rat liver (Werner et al. 1996).

The relative flux of trichloroethylene through the cytochrome P450-dependant oxidative pathway versus the GSH-dependent conjugation pathway is uncertain, although the GSH-dependent pathway is quantitatively minor. These pathways are in competition with each other; inhibition of cytochrome P450 mediated oxidation *in vitro* with renal preparations increases the GSH conjugation of trichloroethylene

(Cummings and Lash 2000). The quantitative reliability of reported concentrations of metabolites of either pathway and of rates of GSH conjugation have been questioned because they vary greatly across studies; it has been suggested that the variance in rates of GSH conjugation may be related to different analytical methods (EPA 2011e).

There is evidence to suggest that trichloroethylene is metabolized in the male reproductive tract, primarily in the epididymal epithelium but also in testicular Leydig cells, by CYP2E1 to chloral, trichloroethanol, and TCA (Forkert et al. 2002, 2003). Furthermore, DCA protein adducts have been detected in the epididymis and efferent ducts of rats administered trichloroethylene (DuTeaux et al. 2003, 2004).

3.4.4 Elimination and Excretion

Additional information regarding metabolites excreted in the urine was summarized in Section 3.4.3 due to its relevance to metabolism.

3.4.4.1 Inhalation Exposure

Following inhalation exposure to trichloroethylene in humans, the unmetabolized parent compound is exhaled, whereas its metabolites are primarily eliminated in the urine. Excretion of trichloroethylene in the bile apparently represents a minor pathway of elimination. Balance studies in humans have shown that following single or sequential daily exposures of 50–380 ppm trichloroethylene, 11 and 2% of the dose was eliminated unchanged and as trichloroethanol, respectively, in the lungs; 58% was eliminated as urinary metabolites; and approximately 30% was unaccounted for (Monster et al. 1976, 1979). The half-lives for trichloroethylene and trichloroethanol in exhaled air were approximately 10 and 20 hours, respectively (Monster et al. 1976). Exhaled air contained notable concentrations of trichloroethylene 18 hours after exposure ended because of the relatively long half-life for elimination of trichloroethylene from the adipose tissue (i.e., 3.5–5 hours) compared to other tissues (Fernandez et al. 1977; Monster et al. 1979). Following exposure of human subjects to 1 ppm for 6 hours, terminal half-lives for trichloroethylene in alveolar air of 14–23 hours were determined (Chiu et al. 2007).

The primary urinary metabolites of trichloroethylene in humans are trichloroethanol, trichloroethanol glucuronide, and TCA (Monster et al. 1979; Nomiyama and Nomiyama 1971; Sato et al. 1977). The half-time for renal elimination of trichloroethanol and trichloroethanol glucuronide has been determined in several studies to be approximately 10 hours following trichloroethylene exposure (Monster et al. 1979; Sato et al. 1977). The renal elimination of TCA is much slower because the metabolite is very tightly and

extensively bound to plasma proteins; data from several studies indicate that the half-time for TCA is approximately 52 hours (Monster et al. 1976; Sato et al. 1977).

Sex differences in the urinary excretion of metabolites of trichloroethylene have been reported (Inoue et al. 1989; Nomiyama and Nomiyama 1971). In trichloroethylene-exposed workers, urinary levels of trichloroethanol were significantly higher in men than in women, while urinary levels of TCA did not differ between the two sexes (Inoue et al. 1989). However, it was reported that excretion of TCA in urine was greater in women than in men within 24 hours of exposure (Nomiyama and Nomiyama 1971).

The radioactivity in urine, feces, and expired breath was evaluated following exposure of mice and rats to [^{14}C]-radiolabelled trichloroethylene (Stott et al. 1982). During 50 hours of evaluation following a 6-hour exposure of mice to trichloroethylene at 10 ppm, 74% of the radioactivity was excreted in the urine, 9% was exhaled as carbon dioxide, and 4% was recovered in the feces. In similarly exposed rats, 63% was recovered in urine, 5% as exhaled carbon dioxide, and 7% in the feces. Exposure at 600 ppm resulted in similar recoveries in urine, expired air, and feces of mice, and slightly less radioactivity in the urine, expired air, and feces of rats.

3.4.4.2 Oral Exposure

A study in two Finnish villages with up to 220 ppb trichloroethylene and/or up to 180 ppb tetrachloroethylene in their drinking water found urinary TCA levels in exposed individuals to be 3–10 times higher (7.9–19 μg/day) than in unexposed controls (2–4 μg/day) (Vartiainen et al. 1993). Besides drinking the water, individuals may have been exposed to these chemicals dermally or through inhalation while bathing. TCA is a metabolite of trichloroethylene as well as tetrachloroethylene.

Seventy-two hours after a single oral dose of 2, 20, or 200 mg/kg [^{14}C]-trichloroethylene was administered to mice and rats, trichloroethylene was eliminated unchanged in exhaled air and urine, whereas the metabolites were excreted primarily in the urine (Dekant et al. 1986b). In rats, the three metabolites that accounted for approximately 90% of the total trichloroethylene urinary metabolites were TCA (15%), trichloroethanol (12%), and conjugated trichloroethanol (62%) (Dekant et al. 1984). Minor urinary metabolites in the rat (i.e., <10% of the total urinary metabolites) were oxalic acid (1.3%), DCA (2.0%), and N-(hydroxyacetyl)-aminoethanol (7.2%). In addition, 1.9% of the absorbed radiolabelled dose was found in the exhaled air as carbon dioxide in rats (Dekant et al. 1984). Male rats that consumed 0.4 mg/kg trichloroethylene from the drinking water containing 4.8 ppm of [^{14}C]-trichloroethylene

excreted 85% of the radioactivity (Koizumi et al. 1986). The percentage of radioactivity excreted in the urine was 40%, while 10.9% was in expired air as carbon dioxide, and 34.6% was in the feces, carcass, and cage wash. About 14.5% was excreted unchanged in the expired air. Four metabolites were characterized in the urine; three of these were identified as TCA, trichloroethanol, and the glucuronide conjugate of trichloroethanol and accounted for 13.1, 2.7, and 81.5% of the radioactivity excreted in the urine, respectively. An unidentified urinary metabolite accounted for 2.7% of the radioactivity (Koizumi et al. 1986).

Excretion data show that saturability of trichloroethylene metabolism occurs at lower exposure levels for rats than for mice (Dekant et al. 1986b; Prout et al. 1985). In mice receiving a single oral dose of 10, 500, 1,000, or 2,000 mg/kg trichloroethylene, urinary TCA and exhaled carbon dioxide over a 24-hour period were directly proportional to the exposure levels (Prout et al. 1985). In rats, however, the amount of TCA and carbon dioxide excreted increased linearly at ≤1,000 mg/kg trichloroethylene and then started to level off. A study of rats and mice receiving single oral doses of 2, 20, and 200 mg/kg also showed that saturation occurred in mice at higher doses than in rats, as demonstrated by the lower percentage of unchanged trichloroethylene exhaled by mice (9.5%) compared to rats (50.9%) after administration of 200 mg/kg [^{14}C]-trichloroethylene (Dekant et al. 1986b).

3.4.4.3 Dermal Exposure

Peak concentrations of trichloroethylene in expired air (approximately 7 nmol/L) occurred approximately 30 minutes following the initiation of exposure of the forearm and hand (1,000 cm^2) of volunteers to trichloroethylene vapor at 1.3 mmol/L (3.18x10^4 ppm) in a dynamic exposure cylinder for 20 minutes (Kezic et al. 2000). Trichloroethylene also was excreted in the breath of volunteers who were exposed dermally to trichloroethylene in water or soil as described in Section 3.4.1.3, generally with a slight delay (0.1–0.55 hours) thought to be due to loading of the chemical into the stratum corneum, and reaching peak levels within about 1 hour after the start of exposure (Poet et al. 2000). Elevated trichloroethylene levels in expired air were measured in subjects who immersed one hand in an unspecified concentration of trichloroethylene in water for 30 minutes (Sato and Nakajima 1978). Volunteers exposed dermally to pure trichloroethylene liquid for 1 minute expired trichloroethylene into the air; the expired air data were used to model permeation rates but were not reported (Kezic et al. 2001).

Guinea pigs, exposed to dilute concentrations of aqueous trichloroethylene (≈0.020–0.110 ppm) over a majority of their body surface area for 70 minutes, excreted 59% of the administered dose in the urine and

feces (data were reported only as combined urine and fecal excretion); 95% of the metabolized dose was excreted in 8.6 days (Bogen et al. 1992). Rats exposed dermally to trichloroethylene in water and soil as described in Section 3.4.1.3 excreted trichloroethylene in the expired air with peak concentrations occurring within 2 hours of the initiation of exposure to trichloroethylene in water and 1–2 hours of exposure to trichloroethylene in soil (Poet et al. 2000). Other excretory routes were not investigated.

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

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

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

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

provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

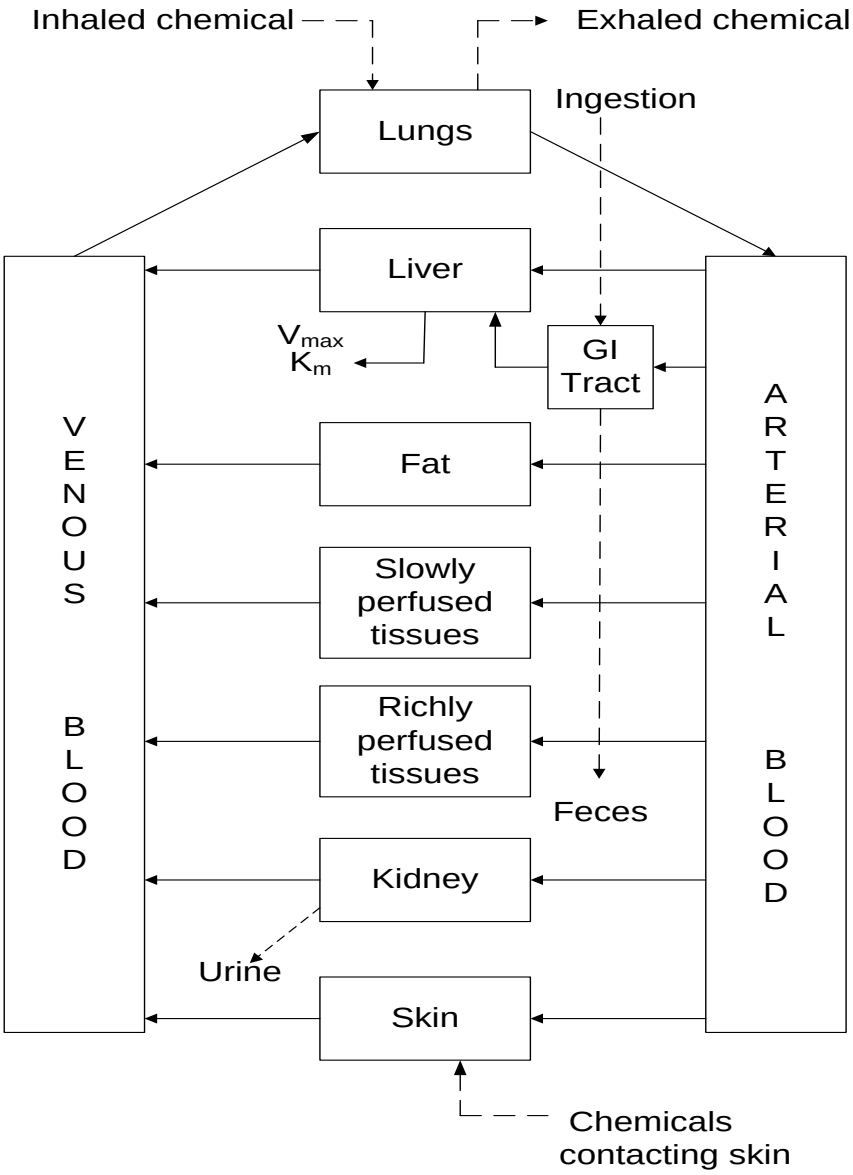
The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. However, if the uptake and disposition of the chemical substance(s) are adequately described, this simplification is desirable because data are often unavailable for many 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 3-22 shows a conceptualized representation of a PBPK model.

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

Several PBPK models of trichloroethylene have been reported that have evolved in complexity to address specific problems in toxicokinetics extrapolation among rats, mice, and humans (Chiu et al. 2009; EPA 2011e; Evans et al. 2009; Fisher 2000; Hack et al. 2006; Keys et al. 2003; Poet et al. 2000; Simmons et al. 2002; Thrall and Poet 2000). The models have focused on descriptions of trichloroethylene and its major oxidative metabolites, TCA, trichloroethanol, and trichloroethanol-glucuronide conjugate. In the early models applied to dosimetry extrapolations, absorbed trichloroethylene was distributed into four flow-limited tissue compartments (liver, fat, rapidly perfused tissue, and slowly perfused tissue), and elimination was attributed to metabolism of trichloroethylene (K_m, V_{max}) in liver (Allen and Fisher 1993; Fisher and Allen 1993; Fisher et al. 1991). Metabolic production of TCA was represented as a fixed proportion of total metabolism and plasma kinetics of TCA was represented with a single-compartment, first-order model. Subsequent models extended the metabolism simulation to include more complete simulations of metabolism and of the metabolites formed (Abbas and Fisher 1997; Greenberg et al. 1999; Fisher et al. 1998). Trichloroethylene metabolism was attributed to conversion to chloral in liver (K_m,

Figure 3-22. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



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

Source: Krishnan and Andersen 1994

V_{max}), and formation of downstream metabolites (DCA, TCA, trichloroethanol, and trichloroethanol-glucuronide conjugate) were presented with first-order rate constants (k_i). These included conversion of chloral to TCA, interconversion of chloral and trichloroethanol, conjugation of trichloroethanol to trichloroethanol-glucuronide conjugate, and conversion of TCA to DCA. Kinetics of each metabolite were simulated with multi-compartment sub-models (e.g., flow-limited liver, fat, rapidly perfused and slowly perfused tissue compartments). The models also included first-order excretion of chloral, TCA, trichloroethanol, and trichloroethanol-glucuronide conjugate, and fecal excretion (i.e., biliary) of trichloroethanol-glucuronide conjugate.

An alternative to models of Fisher and colleagues was developed by Clewell et al. (2000) to specifically address dosimetry predictions of carcinogenicity in target tissues (lung, kidney, and liver). The Clewell et al. (2000) model distributes absorbed trichloroethylene into seven flow-limited tissue compartments (tracheobronchial region of the respiratory tract, gastrointestinal tract, kidney, liver, fat, and rapidly perfused and slowly perfused tissues). Metabolism is assumed to occur in the respiratory tract, kidney, and liver. Metabolism occurring in the respiratory tract includes oxidation of trichloroethylene to chloral (K_m, V_{max}) and metabolic elimination of chloral (K_m, V_{max}). The model assumes that all GSH conjugation of trichloroethylene in the liver or kidney leads to the appearance of DCVC (first order) in the kidney where DCVC is activated to a cytotoxic product (first order) or eliminated in the urine by conversion to NAcDCVC (first order). Liver metabolism is assumed to produce three metabolites (TCA, trichloro-ethanol-glucuronide conjugate, and DCA) which are excreted in urine (first order). These three metabolites are also assumed to be distributed in volumes of distribution (fraction of body weight), which provides for computation of their respective concentrations in blood and plasma. In the liver, trichloroethylene is converted to chloral (K_m, V_{max}), which is instantly and completely converted to TCA or trichloroethanol (proportionality constant). TCA is converted to DCA (K_m, V_{max}). Trichloroethanol undergoes three competing reactions consisting of conversion to TCA (K_m, V_{max}), trichloroethanol-glucuronide conjugate (K_m, V_{max}), or DCA (K_m, V_{max}). Trichloroethanol-glucuronide conjugate, in addition to being excreted in urine, is transferred to the gastrointestinal tract (first order), representing biliary secretion, from where it can be reabsorbed as trichloroethanol (first order), representing enterohepatic circulation. DCA, in addition to being excreted in urine, undergoes metabolic elimination (K_m, V_{max}).

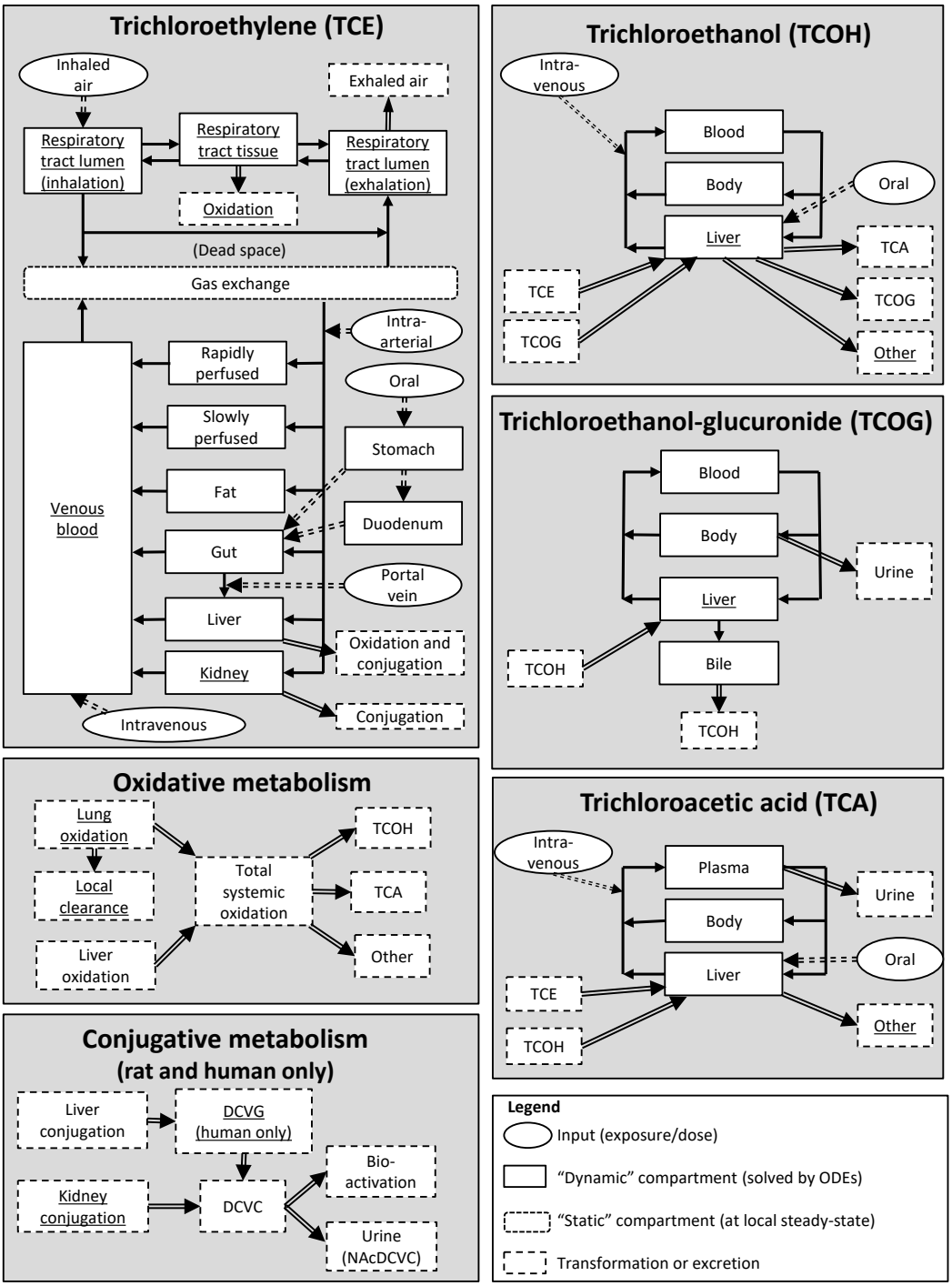
Although the Clewell et al. (2000) and Fisher (2000) models differ in many ways, the major differences are the inclusion of separate tissue compartments for metabolism in respiratory tract, kidney, and liver in the Clewell et al. (2000) model, the inclusion of GSH-dependent DCVC production, activation, and

elimination in the Clewell et al. (2000) model, and flow-limited distribution of trichloroethylene metabolites from blood to tissue compartments in the Fisher (2000) models. The two groups also used different data sets and approaches to estimating model parameters and evaluating model performance. Various statistical analyses, including Bayesian probabilistic approaches to parameter value estimation and uncertainty analyses have been performed on both models (Bois 2000a, 2000b). In 2006, the results of an EPA-U.S. Air Force (USAF) working group included a proposed structure for a harmonized model based on data included in the development of the Fisher (2000) and Clewell et al. (2000) models, along with newer data available at that time (AFRL 2004). Hack et al. (2006) also applied a Bayesian probabilistic approach to estimate parameter values for the harmonized model. The EPA reevaluated the Hack et al. (2006) model and derived a model based on newer data (Chiu et al. 2009; Evans et al. 2009). EPA re-estimated parameter values for the Chiu et al. model (Chiu et al. 2009; Evans et al. 2009) and applied the updated model to dosimetry extrapolations in support of its Toxicological Review of Trichloroethylene (EPA 2011e). The model described in EPA (2011e) is presented below in greater detail because it represents the most recent elaboration of a PBPK model for trichloroethylene for application in risk assessment. It is essentially identical to that described in Chiu et al. (2009) with small differences in the prior and posterior distributions for the central estimates (i.e., median) of parameters.

EPA Model (EPA 2011e; Chiu et al. 2009; Evans et al. 2009).

Description of the Model. The structure of the EPA (2011e) model is shown in Figure 3-23 and parameters and values for rats, mice, and humans are listed in Tables 3-7, 3-8, and 3-9. This model includes eight tissue compartments; it retains the seven-compartment structure of the Clewell et al. (2000) model (tracheobronchial region of the respiratory tract, gastrointestinal tract, kidney, liver, fat, and rapidly perfused and slowly perfused tissues) with the addition of a separate venous blood compartment. Similar to the Clewell et al. (2000) model, metabolism is assumed to occur in the respiratory tract, kidney, and liver. Metabolism occurring in the respiratory tract consists of trichloroethylene oxidation (K_m, V_{max}), with a fraction of oxidative flux undergoing instantaneous elimination within the respiratory tract or translocation to liver where further metabolism to TCA or trichloroethanol occurs. In kidney, trichloroethylene is converted to the GSH conjugate DCVG (K_m, V_{max}), which undergoes conversion to DCVC (first order), which can be activated to a cytotoxic product (first order) or eliminated by conversion to NAcDCVC and excreted in urine (first order). Inclusion of DCVG as a distinct intermediate in the production of DCVC distinguishes the kidney metabolism model in the EPA (2011e) model from other previous models and enables the use of data on DCVG kinetics in parameter estimation (Chiu et al. 2009). Unlike previous models that assume that DCVC production is limited to the kidney,

Figure 3-23. Overall Structure of PBPK Model for Trichloroethylene and Metabolites



Boxes with underlined labels are additions or modifications of the Hack et al. (2006) model.

DCVC = S-dichlorovinylcysteine; DCVG = S-dichlorovinyl-glutathione; NAcTCVC = N-acetyl trichlorovinyl cysteine; ODE = ordinary differential equation

Source: EPA 2011e

Table 3-7. Prior and Posterior Uncertainty and Variability in Mouse PBPK Model Parameters

Parameter description	PBPK parameter	Prior population median: median (2.5%, 97.5%)	Posterior population median: median (2.5%, 97.5%)	Prior population GSD: median (2.5%, 97.5%)	Posterior population GSD: median (2.5%, 97.5%)
Cardiac output (L/hour)	QC	0.84 (0.59, 1.2)	1 (0.79, 1.3)	1.17 (1.1, 1.4)	1.35 (1.15, 1.54)
Alveolar ventilation (L/hour)	QP	2.1 (1.3, 3.5)	2.1 (1.5, 2.7)	1.27 (1.17, 1.54)	1.45 (1.28, 1.66)
Scaled fat blood flow	QFatC	0.07 (0.03, 0.11)	0.072 (0.044, 0.1)	1.65 (1.22, 2.03)	1.64 (1.3, 1.99)
Scaled gut blood flow	QGutC	0.14 (0.11, 0.17)	0.16 (0.14, 0.17)	1.15 (1.09, 1.19)	1.12 (1.07, 1.19)
Scaled liver blood flow	QLivC	0.02 (0.016, 0.024)	0.021 (0.017, 0.024)	1.15 (1.09, 1.19)	1.15 (1.09, 1.19)
Scaled slowly perfused blood flow	QSlwC	0.22 (0.14, 0.29)	0.21 (0.15, 0.28)	1.3 (1.15, 1.38)	1.3 (1.17, 1.39)
Scaled rapidly perfused blood flow	QRapC	0.46 (0.37, 0.56)	0.45 (0.37, 0.52)	1.15 (1.11, 1.2)	1.17 (1.12, 1.2)
Scaled kidney blood flow	QKidC	0.092 (0.054, 0.13)	0.091 (0.064, 0.12)	1.34 (1.14, 1.45)	1.34 (1.18, 1.44)
Respiratory lumen:tissue diffusive clearance rate (L/hour)	DResp	0.017 (0.000032, 15)	2.5 (1.4, 5.1)	1.37 (1.25, 1.62)	1.53 (1.37, 1.73)
Fat fractional compartment volume	VFatC	0.071 (0.032, 0.11)	0.089 (0.061, 0.11)	1.59 (1.19, 1.93)	1.4 (1.19, 1.78)
Gut fractional compartment volume	VGutC	0.049 (0.041, 0.057)	0.048 (0.042, 0.055)	1.11 (1.07, 1.14)	1.11 (1.08, 1.14)
Liver fractional compartment volume	VLivC	0.054 (0.038, 0.071)	0.047 (0.037, 0.06)	1.22 (1.12, 1.29)	1.23 (1.17, 1.3)
Rapidly perfused fractional compartment volume	VRapC	0.1 (0.087, 0.11)	0.099 (0.09, 0.11)	1.08 (1.05, 1.11)	1.09 (1.06, 1.11)
Fractional volume of respiratory lumen	VRespLumC	0.0047 (0.004, 0.0053)	0.0047 (0.0041, 0.0052)	1.09 (1.06, 1.12)	1.09 (1.07, 1.12)
Fractional volume of respiratory tissue	VRespEffC	0.0007 (0.0006, 0.00079)	0.0007 (0.00062, 0.00078)	1.09 (1.06, 1.12)	1.1 (1.07, 1.12)

Table 3-7. Prior and Posterior Uncertainty and Variability in Mouse PBPK Model Parameters

Parameter description	PBPK parameter	Prior population median: median (2.5%, 97.5%)	Posterior population median: median (2.5%, 97.5%)	Prior population GSD: median (2.5%, 97.5%)	Posterior population GSD: median (2.5%, 97.5%)
Kidney fractional compartment volume	VKidC	0.017 (0.015, 0.019)	0.017 (0.015, 0.019)	1.08 (1.05, 1.11)	1.09 (1.06, 1.11)
Blood fractional compartment volume	VBldC	0.049 (0.042, 0.056)	0.048 (0.043, 0.054)	1.1 (1.06, 1.13)	1.1 (1.08, 1.13)
Slowly perfused fractional compartment volume	VSlwC	0.55 (0.5, 0.59)	0.54 (0.51, 0.57)	1.05 (1.04, 1.07)	1.05 (1.04, 1.07)
Plasma fractional compartment volume	VPlasC	0.026 (0.016, 0.036)	0.022 (0.016, 0.029)	1.24 (1.15, 1.35)	1.27 (1.19, 1.36)
TCA body fractional compartment volume (not including blood+liver)	VBodC	0.79 (0.77, 0.8)	0.79 (0.78, 0.81)	1.01 (1.01, 1.02)	1.01 (1.01, 1.02)
TCOH/G body fractional compartment volume (not including liver)	VBodTCOHC	0.84 (0.82, 0.85)	0.84 (0.83, 0.85)	1.01 (1.01, 1.02)	1.01 (1.01, 1.02)
TCE blood:air partition coefficient	PB	15 (10, 23)	14 (11, 17)	1.22 (1.12, 1.42)	1.44 (1.28, 1.53)
TCE fat:blood partition coefficient	PFat	36 (21, 62)	36 (26, 49)	1.26 (1.14, 1.52)	1.32 (1.16, 1.56)
TCE gut:blood partition coefficient	PGut	1.9 (0.89, 3.8)	1.5 (0.94, 2.6)	1.36 (1.2, 1.75)	1.36 (1.2, 1.79)
TCE liver:blood partition coefficient	PLiv	1.7 (0.89, 3.5)	2.2 (1.3, 3.3)	1.37 (1.2, 1.75)	1.39 (1.21, 1.84)
TCE rapidly perfused:blood partition coefficient	PRap	1.8 (0.98, 3.7)	1.8 (1.1, 3)	1.37 (1.2, 1.76)	1.37 (1.2, 1.77)
TCE respiratory tissue:air partition coefficient	PResp	2.7 (1.2, 5)	2.5 (1.5, 4.2)	1.36 (1.19, 1.78)	1.37 (1.19, 1.74)
TCE kidney:blood partition coefficient	PKid	2.2 (0.96, 4.6)	2.6 (1.7, 4)	1.36 (1.2, 1.77)	1.51 (1.25, 1.88)
TCE slowly perfused:blood partition coefficient	PSlw	2.4 (1.2, 4.9)	2.2 (1.4, 3.5)	1.38 (1.2, 1.78)	1.39 (1.21, 1.8)

Table 3-7. Prior and Posterior Uncertainty and Variability in Mouse PBPK Model Parameters

Parameter description	PBPK parameter	Prior population median: median (2.5%, 97.5%)	Posterior population median: median (2.5%, 97.5%)	Prior population GSD: median (2.5%, 97.5%)	Posterior population GSD: median (2.5%, 97.5%)
TCA blood:plasma concentration ratio	TCAPlas	0.76 (0.4, 16)	1.1 (0.75, 1.8)	1.21 (1.09, 1.58)	1.23 (1.1, 1.73)
Free TCA body:blood plasma partition coefficient	PBodTCA	0.77 (0.27, 17)	0.87 (0.59, 1.5)	1.41 (1.23, 1.8)	1.39 (1.24, 1.9)
Free TCA liver:blood plasma partition coefficient	PLivTCA	1.1 (0.36, 21)	1.1 (0.64, 1.9)	1.41 (1.23, 1.8)	1.4 (1.24, 1.87)
Protein:TCA dissociation constant (μmole/L)	kDissoc	100 (13, 790)	130 (24, 520)	2.44 (1.73, 5.42)	2.64 (1.75, 5.45)
Maximum binding concentration (μmole/L)	B_{MAX}	87 (9.6, 790)	140 (28, 690)	2.72 (1.92, 5.78)	2.88 (1.93, 5.89)
TCOH body:blood partition coefficient	PBodTCOH	1.1 (0.61, 2.1)	0.89 (0.65, 1.3)	1.29 (1.16, 1.66)	1.31 (1.17, 1.61)
TCOH liver:body partition coefficient	PLivTCOH	1.3 (0.73, 2.3)	1.9 (1.2, 2.6)	1.3 (1.16, 1.61)	1.35 (1.18, 1.68)
TCOG body:blood partition coefficient	PBodTCOG	0.95 (0.016, 77)	0.48 (0.18, 1.1)	1.36 (1.19, 2.05)	1.41 (1.22, 2.19)
TCOG liver:body partition coefficient	PLivTCOG	1.3 (0.019, 92)	1.3 (0.64, 2.6)	1.36 (1.18, 2.13)	1.56 (1.28, 2.52)
DCVG effective volume of distribution	VDCVG	0.033 (0.0015, 15)	0.027 (0.0016, 4.1)	1.28 (1.08, 1.97)	1.31 (1.1, 2.19)
TCE stomach absorption coefficient (/hour)	kAS	1.7 (0.0049, 450)	1.7 (0.37, 13)	4.74 (2.29, 23.4)	4.28 (2.39, 13.4)
TCE stomach-duodenum transfer coefficient (/hour)	kTSD	1.4 (0.043, 51)	4.5 (0.51, 26)	3.84 (2.09, 10.6)	4.79 (2.53, 10.9)
TCE duodenum absorption coefficient (/hour)	kAD	1.2 (0.0024, 200)	0.27 (0.067, 1.6)	4.33 (2.14, 26)	4.17 (2.34, 14.4)
TCA stomach absorption coefficient (/hour)	kASTCA	0.63 (0.0027, 240)	4 (0.2, 74)	4.26 (2.27, 23.4)	5.15 (2.56, 22)
V_{MAX} for hepatic TCE oxidation (mg/hour)	V_{MAX}	3.9 (1.4, 15)	2.5 (1.6, 4.2)	2.02 (1.56, 2.85)	1.86 (1.59, 2.47)

Table 3-7. Prior and Posterior Uncertainty and Variability in Mouse PBPK Model Parameters

Parameter description	PBPK parameter	Prior population median: median (2.5%, 97.5%)	Posterior population median: median (2.5%, 97.5%)	Prior population GSD: median (2.5%, 97.5%)	Posterior population GSD: median (2.5%, 97.5%)
K_M for hepatic TCE oxidation (mg/L)	K_M	34 (1.6, 620)	2.7 (1.4, 8)	1.25 (1.15, 1.61)	2.08 (1.48, 3.49)
Fraction of hepatic TCE oxidation not to TCA+TCOH	FracOther	0.43 (0.0018, 1)	0.023 (0.0037, 0.15)	1.23 (1, 2.13)	1.49 (1.25, 2.83)
Fraction of hepatic TCE oxidation to TCA	FracTCA	0.086 (0.00022, 0.66)	0.13 (0.084, 0.21)	1.48 (1.12, 2.56)	1.4 (1.21, 1.96)
V_{MAX} for hepatic TCE GSH conjugation (mg/hour)	V_{MAX} DCVG	3.7 (0.0071, 2,800)	0.6 (0.01, 480)	1.55 (1.33, 2.52)	1.61 (1.37, 2.91)
K_M for hepatic TCE GSH conjugation (mg/L)	K_MDCVG	250 (0.0029, 6,500,000)	2,200 (0.17, 2,300,000)	1.81 (1.47, 3.62)	1.93 (1.49, 3.68)
V_{MAX} for renal TCE GSH conjugation (mg/hour)	V_{MAX} KidDCVG	0.34 (0.00051, 180)	0.027 (0.0012, 13)	1.49 (1.26, 2.49)	1.54 (1.28, 2.72)
K_M for renal TCE GSH conjugation (mg/L)	K_MKidDCVG	150 (0.0053, 6,200,000)	160 (0.078, 280,000)	1.79 (1.43, 3.45)	1.91 (1.5, 3.91)
V_{MAX} for tracheo-bronchial TCE oxidation (mg/hour)	V_{MAX} Clara	0.24 (0.03, 3.9)	0.42 (0.1, 1.5)	2.32 (1.74, 3.66)	4.13 (2.27, 6.79)
K_M for tracheo-bronchial TCE oxidation (mg/L)	K_MClara	1.5 (0.0018, 630)	0.011 (0.0024, 0.09)	1.47 (1.25, 2.58)	1.63 (1.28, 5.02)
Fraction of respiratory metabolism to systemic circulation	FracLungSys	0.34 (0.0016, 1)	0.78 (0.18, 0.99)	1.24 (1, 2.1)	1.11 (1, 1.72)
V_{MAX} for hepatic TCOH→TCA (mg/hour)	V_{MAX} TCOH	0.064 (0.000014, 380)	0.12 (0.048, 0.28)	1.5 (1.24, 2.61)	1.6 (1.28, 2.92)
K_M for hepatic TCOH→TCA (mg/L)	K_MTCOH	1.4 (0.00018, 5,300)	0.92 (0.26, 2.7)	1.48 (1.24, 2.41)	1.49 (1.26, 2.4)

Table 3-7. Prior and Posterior Uncertainty and Variability in Mouse PBPK Model Parameters

Parameter description	PBPK parameter	Prior population median: median (2.5%, 97.5%)	Posterior population median: median (2.5%, 97.5%)	Prior population GSD: median (2.5%, 97.5%)	Posterior population GSD: median (2.5%, 97.5%)
V_{MAX} for hepatic TCOH→TCOG (mg/hour)	V_{MAX} Gluc	0.11 (0.000013, 310)	4.6 (1.9, 16)	1.48 (1.26, 2.53)	1.47 (1.26, 2.14)
K_M for hepatic TCOH→TCOG (mg/L)	K_MGluc	1.8 (0.0018, 610)	30 (5.3, 130)	1.48 (1.25, 2.48)	1.8 (1.3, 4.72)
Rate constant for hepatic TCOH→other (/hour)	kMetTCOH	0.19 (0.000039, 1,400)	8.8 (1.9, 23)	1.47 (1.25, 2.36)	1.54 (1.26, 2.92)
Rate constant for TCA plasma→urine (/hour)	kUrnTCA	32 (0.38, 1,700)	3.2 (1.2, 7.1)	1.57 (1.34, 2.61)	1.84 (1.44, 2.94)
Rate constant for hepatic TCA→other (/hour)	kMetTCA	0.12 (0.0004, 130)	1.5 (0.63, 2.9)	1.48 (1.25, 2.32)	1.51 (1.26, 2.27)
Rate constant for TCOG liver→bile (/hour)	kBile	0.3 (0.0004, 160)	2.4 (0.74, 8.4)	1.48 (1.24, 2.29)	1.51 (1.26, 2.39)
Lumped rate constant for TCOG bile→TCOH liver (/hour)	kEHR	0.21 (0.00036, 150)	0.039 (0.0026, 0.11)	1.47 (1.23, 2.29)	1.53 (1.28, 2.94)
Rate constant for TCOG→urine (/hour)	kUrnTCOG	1 (0.00015, 6200)	12 (2.6, 77)	1.71 (1.4, 3.13)	3.44 (1.89, 9.49)
Rate constant for hepatic DCVG→DCVC (/hour)	kDCVG	0.24 (0.0004, 160)	0.81 (0.0033, 46)	1.48 (1.25, 2.39)	1.52 (1.25, 2.5)
Lumped rate constant for DCVC→urinary NAcDCVC (/hour)	kNAT	0.29 (0.0004, 160)	0.37 (0.0021, 34)	1.5 (1.25, 2.49)	1.53 (1.25, 2.77)
Rate constant for DCVC bioactivation (/hour)	kKidBioact	0.18 (0.0004, 150)	0.23 (0.0024, 33)	1.48 (1.25, 2.51)	1.53 (1.25, 3.03)

Source: EPA 2011e

Table 3-8. Prior and Posterior Uncertainty and Variability in Rat PBPK Model Parameters

Parameter description	PBPK parameter	Prior population median: median (2.5%, 97.5%)	Posterior population median: median (2.5%, 97.5%)	Prior population GSD: median (2.5%, 97.5%)	Posterior population GSD: median (2.5%, 97.5%)
Cardiac output (L/hour)	QC	5.3 (4.2, 6.9)	6.1 (5.2, 7.4)	1.12 (1.07, 1.28)	1.26 (1.12, 1.36)
Alveolar ventilation (L/hour)	QP	10 (5.1, 18)	7.5 (5.8, 10)	1.32 (1.18, 1.71)	1.52 (1.33, 1.84)
Scaled fat blood flow	QFatC	0.071 (0.032, 0.11)	0.081 (0.06, 0.1)	1.66 (1.21, 2.02)	1.5 (1.3, 1.86)
Scaled gut blood flow	QGutC	0.15 (0.12, 0.18)	0.17 (0.15, 0.19)	1.15 (1.09, 1.19)	1.13 (1.08, 1.18)
Scaled liver blood flow	QLivC	0.021 (0.017, 0.026)	0.022 (0.018, 0.025)	1.15 (1.09, 1.2)	1.15 (1.1, 1.19)
Scaled slowly perfused blood flow	QSlwC	0.33 (0.21, 0.46)	0.31 (0.23, 0.4)	1.31 (1.15, 1.4)	1.32 (1.22, 1.41)
Scaled rapidly perfused blood flow	QRapC	0.28 (0.15, 0.42)	0.28 (0.18, 0.36)	1.38 (0.0777, 1.72)	1.42 (0.0856, 1.75)
Scaled kidney blood flow	QKidC	0.14 (0.12, 0.16)	0.14 (0.12, 0.16)	1.11 (1.07, 1.14)	1.11 (1.08, 1.14)
Respiratory lumen:tissue diffusive clearance rate (L/hour)	DResp	9.9 (0.48, 85)	21 (9.5, 46)	1.41 (1.26, 1.77)	1.59 (1.41, 1.9)
Fat fractional compartment volume	VFatC	0.069 (0.031, 0.11)	0.069 (0.046, 0.091)	1.61 (1.2, 1.93)	1.59 (1.34, 1.88)
Gut fractional compartment volume	VGutC	0.032 (0.027, 0.037)	0.032 (0.028, 0.036)	1.11 (1.07, 1.14)	1.11 (1.08, 1.14)
Liver fractional compartment volume	VLivC	0.034 (0.026, 0.042)	0.033 (0.028, 0.039)	1.16 (1.09, 1.21)	1.17 (1.12, 1.21)
Rapidly perfused fractional compartment volume	VRapC	0.087 (0.076, 0.1)	0.088 (0.079, 0.097)	1.1 (1.06, 1.13)	1.1 (1.07, 1.13)
Fractional volume of respiratory lumen	VRespLumC	0.0046 (0.0037, 0.0057)	0.0047 (0.0039, 0.0055)	1.16 (1.1, 1.21)	1.16 (1.11, 1.21)
Fractional volume of respiratory tissue	VRespEffC	0.0005 (0.00039, 0.00061)	0.0005 (0.00041, 0.00058)	1.16 (1.09, 1.21)	1.16 (1.11, 1.2)

Table 3-8. Prior and Posterior Uncertainty and Variability in Rat PBPK Model Parameters

Parameter description	PBPK parameter	Prior population median: median (2.5%, 97.5%)	Posterior population median: median (2.5%, 97.5%)	Prior population GSD: median (2.5%, 97.5%)	Posterior population GSD: median (2.5%, 97.5%)
Kidney fractional compartment volume	VKidC	0.0069 (0.0056, 0.0082)	0.007 (0.006, 0.008)	1.13 (1.08, 1.17)	1.13 (1.09, 1.17)
Blood fractional compartment volume	VBldC	0.073 (0.063, 0.085)	0.074 (0.066, 0.082)	1.1 (1.06, 1.13)	1.1 (1.07, 1.13)
Slowly perfused fractional compartment volume	VSlwC	0.6 (0.55, 0.63)	0.6 (0.57, 0.62)	1.05 (1.04, 1.06)	1.05 (1.04, 1.06)
Plasma fractional compartment volume	VPlasC	0.039 (0.025, 0.054)	0.04 (0.032, 0.049)	1.24 (1.15, 1.35)	1.22 (1.16, 1.33)
TCA body fractional compartment volume (not including blood+liver)	VBodC	0.79 (0.78, 0.81)	0.79 (0.78, 0.8)	1.01 (1.01, 1.01)	1.01 (1.01, 1.01)
TCOH/G body fractional compartment volume (not including liver)	VBodTCOHC	0.87 (0.86, 0.87)	0.87 (0.86, 0.87)	1.01 (1, 1.01)	1.01 (1, 1.01)
TCE blood:air partition coefficient	PB	22 (14, 33)	19 (16, 24)	1.26 (1.19, 1.35)	1.3 (1.22, 1.38)
TCE fat:blood partition coefficient	PFat	27 (16, 46)	31 (24, 42)	1.32 (1.22, 1.44)	1.32 (1.23, 1.43)
TCE gut:blood partition coefficient	PGut	1.3 (0.69, 3)	1.1 (0.79, 1.7)	1.36 (1.21, 1.79)	1.36 (1.2, 1.68)
TCE liver:blood partition coefficient	PLiv	1.5 (1.2, 1.9)	1.6 (1.3, 1.8)	1.15 (1.11, 1.2)	1.15 (1.11, 1.2)
TCE rapidly perfused:blood partition coefficient	PRap	1.3 (0.66, 2.7)	1.3 (0.82, 2.1)	1.35 (1.18, 1.82)	1.37 (1.2, 1.76)
TCE respiratory tissue:air partition coefficient	PResp	0.97 (0.48, 2.1)	1 (0.62, 1.6)	1.37 (1.19, 1.77)	1.36 (1.19, 1.78)
TCE kidney:blood partition coefficient	PKid	1.3 (0.77, 2.2)	1.2 (0.9, 1.7)	1.31 (1.19, 1.5)	1.3 (1.2, 1.45)

Table 3-8. Prior and Posterior Uncertainty and Variability in Rat PBPK Model Parameters

Parameter description	PBPK parameter	Prior population median: median (2.5%, 97.5%)	Posterior population median: median (2.5%, 97.5%)	Prior population GSD: median (2.5%, 97.5%)	Posterior population GSD: median (2.5%, 97.5%)
TCE slowly perfused:blood partition coefficient	PSlw	0.57 (0.35, 0.97)	0.73 (0.54, 0.97)	1.32 (1.23, 1.43)	1.33 (1.25, 1.46)
TCA blood:plasma concentration ratio	TCAPlas	0.78 (0.6, 0.96)	0.78 (0.71, 0.86)	1.12 (1.06, 1.22)	1.11 (1.07, 1.17)
Free TCA body:blood plasma partition coefficient	PBodTCA	0.7 (0.18, 2.2)	0.76 (0.46, 1.3)	1.72 (1.39, 2.81)	1.65 (1.4, 2.19)
Free TCA liver:blood plasma partition coefficient	PLivTCA	0.84 (0.25, 3.3)	1.1 (0.61, 2.1)	1.71 (1.39, 2.78)	1.66 (1.38, 2.37)
Protein:TCA dissociation constant (μmole/L)	kDissoc	270 (95, 790)	280 (140, 530)	1.62 (1.31, 2.43)	1.6 (1.31, 2.31)
Maximum binding concentration (μmole/L)	B_{MAX}	320 (80, 1300)	320 (130, 750)	1.89 (1.5, 2.64)	1.84 (1.49, 2.57)
TCOH body:blood partition coefficient	PBodTCOH	1 (0.33, 4)	1.1 (0.51, 2.1)	1.71 (1.37, 2.69)	1.76 (1.38, 2.45)
TCOH liver:body partition coefficient	PLivTCOH	1.3 (0.39, 4.5)	1.2 (0.59, 2.8)	1.71 (1.37, 2.8)	1.78 (1.37, 2.75)
TCOG body:blood partition coefficient	PBodTCOG	0.48 (0.021, 14)	1.6 (0.091, 16)	1.39 (1.2, 1.97)	1.42 (1.21, 2.52)
TCOG liver:body partition coefficient	PLivTCOG	1.3 (0.078, 39)	10 (2.7, 41)	1.4 (1.2, 2.14)	1.42 (1.21, 2.3)
DCVG effective volume of distribution	VDCVG	0.27 (0.27, 0.27)	0.27 (0.27, 0.27)	1 (1, 1)	1 (1, 1)
TCE stomach absorption coefficient (/hour)	kAS	0.73 (0.0044, 400)	2.5 (0.32, 19)	4.16 (2.21, 20)	9.3 (4.07, 31.1)
TCE stomach-duodenum transfer coefficient (/hour)	kTSD	1.4 (0.04, 45)	3.2 (0.31, 19)	3.92 (2.13, 10.4)	5.54 (2.77, 10.7)
TCE duodenum absorption coefficient (/hour)	kAD	0.96 (0.0023, 260)	0.17 (0.038, 1)	4.17 (2.15, 20.8)	4.07 (2.51, 11.9)

Table 3-8. Prior and Posterior Uncertainty and Variability in Rat PBPK Model Parameters

Parameter description	PBPK parameter	Prior population median: median (2.5%, 97.5%)	Posterior population median: median (2.5%, 97.5%)	Prior population GSD: median (2.5%, 97.5%)	Posterior population GSD: median (2.5%, 97.5%)
TCA stomach absorption coefficient (/hour)	kASTCA	0.83 (0.0024, 240)	1.4 (0.13, 13)	4.15 (2.2, 18.7)	4.21 (2.4, 11.4)
V_{MAX} for hepatic TCE oxidation (mg/hour)	V_{MAX}	5.8 (2, 19)	5.3 (3.9, 7.7)	1.97 (1.54, 2.92)	1.69 (1.47, 2.15)
K_M for hepatic TCE oxidation (mg/L)	K_M	18 (1.9, 240)	0.74 (0.54, 1.4)	2.76 (1.89, 6.46)	1.84 (1.51, 2.7)
Fraction of hepatic TCE oxidation not to TCA+TCOH	FracOther	0.027 (0.0018, 0.59)	0.29 (0.047, 0.56)	1.42 (1.15, 2.33)	2.15 (1.32, 5.06)
Fraction of hepatic TCE oxidation to TCA	FracTCA	0.2 (0.027, 0.76)	0.046 (0.023, 0.087)	1.35 (1.11, 2.14)	1.84 (1.36, 2.8)
V_{MAX} for hepatic TCE GSH conjugation (mg/hour)	V_{MAX} DCVG	2 (0.015, 1100)	5.8 (0.16, 340)	1.52 (1.3, 2.67)	1.57 (1.32, 2.93)
K_M for hepatic TCE GSH conjugation (mg/L)	K_MDCVG	1,500 (1.2, 1,800,000)	6,300 (120, 720,000)	1.83 (1.45, 3.15)	1.88 (1.48, 3.49)
V_{MAX} for renal TCE GSH conjugation (mg/hour)	V_{MAX} KidDCVG	0.038 (0.00027, 13)	0.0024 (0.0005, 0.014)	1.52 (1.3, 2.81)	1.56 (1.29, 2.72)
K_M for renal TCE GSH conjugation (mg/L)	K_MKidDCVG	470 (0.47, 530,000)	0.25 (0.038, 2.2)	1.84 (1.47, 4.27)	1.93 (1.49, 3.57)
V_{MAX} for tracheo-bronchial TCE oxidation (mg/hour)	V_{MAX} Clara	0.2 (0.0077, 2.4)	0.17 (0.042, 0.69)	2.26 (1.71, 3.3)	4.35 (1.99, 6.7)
K_M for tracheo-bronchial TCE oxidation (mg/L)	K_MClara	0.016 (0.0014, 0.58)	0.025 (0.005, 0.15)	1.47 (1.26, 2.39)	1.65 (1.28, 10.5)
Fraction of respiratory metabolism to systemic circulation	FracLungSys	0.82 (0.027, 1)	0.73 (0.06, 0.98)	1.09 (1, 1.71)	1.13 (1.01, 1.86)

Table 3-8. Prior and Posterior Uncertainty and Variability in Rat PBPK Model Parameters

Parameter description	PBPK parameter	Prior population median: median (2.5%, 97.5%)	Posterior population median: median (2.5%, 97.5%)	Prior population GSD: median (2.5%, 97.5%)	Posterior population GSD: median (2.5%, 97.5%)
V_{MAX} for hepatic TCOH→TCA (mg/hour)	V_{MAX} TCOH	0.75 (0.037, 20)	0.71 (0.27, 2.2)	1.51 (1.25, 2.64)	1.68 (1.3, 3.23)
K_M for hepatic TCOH→TCA (mg/L)	K_MTCOH	1 (0.029, 23)	19 (3.6, 94)	1.52 (1.26, 2.7)	1.72 (1.26, 3.93)
V_{MAX} for hepatic TCOH→TCOG (mg/hour)	V_{MAX} Gluc	27 (0.83, 620)	11 (4.1, 32)	1.5 (1.25, 2.59)	2.3 (1.41, 5.19)
K_M for hepatic TCOH→TCOG (mg/L)	K_MGluc	31 (1, 570)	6.3 (1.2, 20)	1.5 (1.25, 2.74)	2.04 (1.3, 8.4)
Rate constant for hepatic TCOH→other (/hour)	kMetTCOH	4.2 (0.17, 150)	3 (0.57, 15)	1.49 (1.27, 2.67)	1.72 (1.3, 8.31)
Rate constant for TCA plasma→urine (/hour)	kUrnTCA	1.9 (0.21, 47)	0.92 (0.51, 1.7)	1.56 (1.33, 2.81)	1.58 (1.36, 2.25)
Rate constant for hepatic TCA→other (/hour)	kMetTCA	0.76 (0.037, 19)	0.47 (0.17, 1.2)	1.5 (1.26, 2.74)	1.52 (1.27, 2.45)
Rate constant for TCOG liver→bile (/hour)	kBile	1.4 (0.052, 31)	14 (2.7, 39)	1.5 (1.25, 2.8)	1.63 (1.29, 4.1)
Lumped rate constant for TCOG bile→TCOH liver (/hour)	kEHR	0.013 (0.00055, 0.64)	1.7 (0.34, 7.4)	1.5 (1.25, 2.49)	1.67 (1.26, 5.91)
Rate constant for TCOG→urine (/hour)	kUrnTCOG	11 (0.063, 1000)	12 (0.45, 370)	1.74 (1.42, 2.99)	1.86 (1.43, 3.54)
Rate constant for hepatic DCVG→DCVC (/hour)	kDCVG	30,000 (30,000, 30,000)	30,000 (30,000, 30,000)	1 (1, 1)	1 (1, 1)

Table 3-8. Prior and Posterior Uncertainty and Variability in Rat PBPK Model Parameters

Parameter description	PBPK parameter	Prior population median: median (2.5%, 97.5%)	Posterior population median: median (2.5%, 97.5%)	Prior population GSD: median (2.5%, 97.5%)	Posterior population GSD: median (2.5%, 97.5%)
Lumped rate constant for DCVC→urinary NAcDCVC (/hour)	kNAT	0.15 (0.00024, 84)	0.0029 (0.00066, 0.015)	1.49 (1.24, 2.8)	1.54 (1.26, 2.45)
Rate constant for DCVC bioactivation (/hour)	kKidBioact	0.12 (0.00023, 83)	0.0092 (0.0012, 0.043)	1.48 (1.24, 2.68)	1.52 (1.25, 2.5)

Source: EPA 2011e

Table 3-9. Prior and Posterior Uncertainty and Variability in Human PBPK Model Parameters

Parameter description	PBPK parameter	Prior population median: median (2.5%, 97.5%)	Posterior population median: median (2.5%, 97.5%)	Prior population GSD: median (2.5%, 97.5%)	Posterior population GSD: median (2.5%, 97.5%)
Cardiac output (L/hour)	QC	390 (280, 560)	330 (280, 390)	1.17 (1.1, 1.39)	1.39 (1.26, 1.54)
Alveolar ventilation (L/hour)	QP	380 (220, 640)	440 (360, 530)	1.27 (1.17, 1.52)	1.58 (1.44, 1.73)
Scaled fat blood flow	QFatC	0.051 (0.021, 0.078)	0.043 (0.033, 0.055)	1.64 (1.23, 2)	1.92 (1.72, 2.09)
Scaled gut blood flow	QGutC	0.19 (0.15, 0.23)	0.16 (0.14, 0.18)	1.16 (1.1, 1.21)	1.16 (1.12, 1.2)
Scaled liver blood flow	QLivC	0.063 (0.029, 0.099)	0.039 (0.026, 0.055)	1.62 (1.22, 1.92)	1.8 (1.62, 1.98)
Scaled slowly perfused blood flow	QSlwC	0.22 (0.13, 0.3)	0.17 (0.14, 0.21)	1.34 (1.18, 1.45)	1.39 (1.31, 1.46)
Scaled rapidly perfused blood flow	QRapC	0.29 (0.18, 0.4)	0.39 (0.34, 0.43)	1.31 (1.14, 1.57)	1.22 (1.16, 1.3)
Scaled kidney blood flow	QKidC	0.19 (0.16, 0.22)	0.19 (0.18, 0.21)	1.1 (1.07, 1.13)	1.1 (1.07, 1.12)
Respiratory lumen:tissue diffusive clearance rate (L/hour)	DResp	560 (44, 3300)	270 (130, 470)	1.37 (1.25, 1.61)	1.71 (1.52, 2.35)
Fat fractional compartment volume	VFatC	0.19 (0.088, 0.31)	0.16 (0.12, 0.21)	1.66 (1.23, 1.93)	1.65 (1.4, 1.9)
Gut fractional compartment volume	VGutC	0.02 (0.018, 0.022)	0.02 (0.019, 0.021)	1.07 (1.04, 1.08)	1.06 (1.05, 1.08)
Liver fractional compartment volume	VLivC	0.026 (0.018, 0.032)	0.026 (0.022, 0.03)	1.21 (1.12, 1.28)	1.2 (1.13, 1.26)
Rapidly perfused fractional compartment volume	VRapC	0.087 (0.079, 0.096)	0.088 (0.083, 0.093)	1.07 (1.05, 1.09)	1.06 (1.05, 1.08)
Fractional volume of respiratory lumen	VRespLumC	0.0024 (0.0018, 0.003)	0.0024 (0.0021, 0.0027)	1.18 (1.1, 1.23)	1.17 (1.12, 1.22)
Fractional volume of respiratory tissue	VRespEffC	0.00018 (0.00014, 0.00022)	0.00018 (0.00015, 0.00021)	1.18 (1.1, 1.24)	1.17 (1.13, 1.23)

Table 3-9. Prior and Posterior Uncertainty and Variability in Human PBPK Model Parameters

Parameter description	PBPK parameter	Prior population median: median (2.5%, 97.5%)	Posterior population median: median (2.5%, 97.5%)	Prior population GSD: median (2.5%, 97.5%)	Posterior population GSD: median (2.5%, 97.5%)
Kidney fractional compartment volume	VKidC	0.0043 (0.0034, 0.0052)	0.0043 (0.0038, 0.0048)	1.15 (1.09, 1.19)	1.14 (1.1, 1.19)
Blood fractional compartment volume	VBldC	0.077 (0.066, 0.088)	0.078 (0.072, 0.084)	1.1 (1.06, 1.13)	1.1 (1.07, 1.13)
Slowly perfused fractional compartment volume	VSlwC	0.45 (0.33, 0.55)	0.48 (0.43, 0.52)	1.18 (1.1, 1.24)	1.16 (1.12, 1.22)
Plasma fractional compartment volume	VPlasC	0.044 (0.037, 0.051)	0.044 (0.04, 0.048)	1.11 (1.08, 1.14)	1.11 (1.08, 1.14)
TCA body fractional compartment volume (not including blood+liver)	VBodC	0.75 (0.74, 0.77)	0.75 (0.74, 0.76)	1.01 (1.01, 1.01)	1.01 (1.01, 1.01)
TCOH/G body fractional compartment volume (not including liver)	VBodTCOHC	0.83 (0.82, 0.84)	0.83 (0.83, 0.83)	1.01 (1, 1.01)	1.01 (1, 1.01)
TCE blood:air partition coefficient	PB	9.6 (6.5, 13)	9.2 (8.2, 10)	1.18 (1.13, 1.26)	1.21 (1.16, 1.28)
TCE fat:blood partition coefficient	PFat	68 (46, 98)	57 (49, 66)	1.18 (1.11, 1.33)	1.18 (1.11, 1.3)
TCE gut:blood partition coefficient	PGut	2.6 (1.3, 5.3)	2.9 (1.9, 4.1)	1.37 (1.2, 1.78)	1.41 (1.21, 1.77)
TCE liver:blood partition coefficient	PLiv	4 (1.9, 8.5)	4.1 (2.7, 5.9)	1.37 (1.22, 1.81)	1.33 (1.19, 1.6)
TCE rapidly perfused:blood partition coefficient	PRap	2.6 (1.2, 5.7)	2.4 (1.8, 3.2)	1.37 (1.21, 1.78)	1.5 (1.25, 1.87)
TCE respiratory tissue:air partition coefficient	PResp	1.3 (0.65, 2.7)	1.3 (0.9, 1.9)	1.36 (1.19, 1.81)	1.32 (1.2, 1.56)
TCE kidney:blood partition coefficient	PKid	1.6 (1.1, 2.3)	1.6 (1.3, 1.9)	1.17 (1.1, 1.33)	1.15 (1.09, 1.25)

Table 3-9. Prior and Posterior Uncertainty and Variability in Human PBPK Model Parameters

Parameter description	PBPK parameter	Prior population median: median (2.5%, 97.5%)	Posterior population median: median (2.5%, 97.5%)	Prior population GSD: median (2.5%, 97.5%)	Posterior population GSD: median (2.5%, 97.5%)
TCE slowly perfused:blood partition coefficient	PSlw	2.1 (1.2, 3.5)	2.3 (1.9, 2.8)	1.28 (1.14, 1.53)	1.51 (1.36, 1.66)
TCA blood:plasma concentration ratio	TCAPlas	0.78 (0.55, 15)	0.65 (0.6, 0.77)	1.08 (1.03, 1.53)	1.52 (1.23, 2.03)
Free TCA body:blood plasma partition coefficient	PBodTCA	0.45 (0.19, 8.1)	0.44 (0.33, 0.55)	1.36 (1.19, 1.75)	1.67 (1.38, 2.2)
Free TCA liver:blood plasma partition coefficient	PLivTCA	0.59 (0.24, 10)	0.55 (0.39, 0.77)	1.36 (1.18, 1.76)	1.65 (1.37, 2.16)
Protein:TCA dissociation constant (μmole/L)	kDissoc	180 (160, 200)	180 (170, 190)	1.05 (1.03, 1.09)	1.04 (1.03, 1.07)
Maximum binding concentration (μmole/L)	B_{MAX}	830 (600, 1100)	740 (630, 880)	1.17 (1.1, 1.3)	1.16 (1.1, 1.28)
TCOH body:blood partition coefficient	PBodTCOH	0.89 (0.51, 1.7)	1.5 (1.3, 1.7)	1.29 (1.16, 1.64)	1.34 (1.25, 1.47)
TCOH liver:body partition coefficient	PLivTCOH	0.58 (0.32, 1.1)	0.63 (0.45, 0.87)	1.29 (1.16, 1.65)	1.29 (1.17, 1.5)
TCOG body:blood partition coefficient	PBodTCOG	0.67 (0.036, 16)	0.72 (0.3, 1.8)	1.38 (1.2, 2.42)	7.83 (4.86, 12.6)
TCOG liver:body partition coefficient	PLivTCOG	1.8 (0.11, 28)	3.1 (0.87, 8.1)	1.38 (1.19, 2.04)	4.94 (2.73, 8.58)
DCVG effective volume of distribution	VDCVG	73 (5.2, 36000)	6.1 (5.4, 7.3)	1.27 (1.08, 1.95)	1.1 (1.07, 1.16)
TCE stomach absorption coefficient (/hour)	kAS	1.4 (1.4, 1.4)	1.4 (1.4, 1.4)	1 (1, 1)	1 (1, 1)
TCE stomach-duodenum transfer coefficient (/hour)	kTSD	1.4 (1.4, 1.4)	1.4 (1.4, 1.4)	1 (1, 1)	1 (1, 1)
TCE duodenum absorption coefficient (/hour)	kAD	0.75 (0.75, 0.75)	0.75 (0.75, 0.75)	1 (1, 1)	1 (1, 1)

Table 3-9. Prior and Posterior Uncertainty and Variability in Human PBPK Model Parameters

Parameter description	PBPK parameter	Prior population median: median (2.5%, 97.5%)	Posterior population median: median (2.5%, 97.5%)	Prior population GSD: median (2.5%, 97.5%)	Posterior population GSD: median (2.5%, 97.5%)
TCA stomach absorption coefficient (/hour)	kASTCA	0.58 (0.0022, 210)	3 (0.061, 180)	4.26 (2.13, 17.6)	5.16 (2.57, 22.3)
TCOH stomach absorption coefficient (/hour)	kASTCOH	0.49 (0.0024, 210)	7.6 (0.11, 150)	4.19 (2.22, 21.5)	5.02 (2.44, 18.5)
V_{MAX} for hepatic TCE oxidation (mg/hour)	V_{MAX}	430 (130, 1500)	190 (130, 290)	1.98 (1.69, 2.31)	2.02 (1.77, 2.38)
K_M for hepatic TCE oxidation (mg/L)	K_M	3.7 (0.22, 63)	0.18 (0.078, 0.4)	2.74 (2.1, 5.62)	4.02 (2.9, 5.64)
Fraction of hepatic TCE oxidation not to TCA+TCOH	FracOther	0.12 (0.0066, 0.7)	0.11 (0.024, 0.23)	1.4 (1.11, 2.38)	2.71 (1.37, 5.33)
Fraction of hepatic TCE oxidation to TCA	FracTCA	0.19 (0.036, 0.56)	0.035 (0.024, 0.05)	2.55 (1.51, 3.96)	2.25 (1.89, 2.87)
V_{MAX} for hepatic TCE GSH conjugation (mg/hour)	V_{MAX} DCVG	100 (0.0057, 690,000)	340 (110, 1100)	1.91 (1.55, 3.76)	6.18 (3.35, 11.3)
K_M for hepatic TCE GSH conjugation (mg/L)	K_MDCVG	3.1 (0.21, 42)	3.6 (1.2, 11)	1.52 (1.26, 2.91)	4.2 (2.48, 8.01)
V_{MAX} for renal TCE GSH conjugation (mg/hour)	V_{MAX} KidDCVG	220 (0.028, 6,700,000)	2.1 (0.17, 9.3)	1.86 (1.51, 3.33)	4.02 (1.57, 33.9)
K_M for renal TCE GSH conjugation (mg/L)	K_MKidDCVG	2.7 (0.14, 41)	0.76 (0.29, 5.8)	1.5 (1.27, 2.56)	1.49 (1.27, 2.32)
V_{MAX} for tracheo-bronchial TCE oxidation (mg/hour)	V_{MAX} Clara	25 (1, 260)	18 (3.8, 41)	2.25 (1.85, 3.25)	2.9 (2.12, 6.49)
K_M for tracheo-bronchial TCE oxidation (mg/L)	K_MClara	0.019 (0.0017, 0.5)	0.31 (0.057, 1.4)	1.48 (1.25, 2.39)	10.8 (1.99, 37.6)

Table 3-9. Prior and Posterior Uncertainty and Variability in Human PBPK Model Parameters

Parameter description	PBPK parameter	Prior population median: median (2.5%, 97.5%)	Posterior population median: median (2.5%, 97.5%)	Prior population GSD: median (2.5%, 97.5%)	Posterior population GSD: median (2.5%, 97.5%)
Fraction of respiratory metabolism to systemic circulation	FracLungSys	0.75 (0.051, 0.99)	0.96 (0.86, 0.99)	1.12 (1, 1.75)	1.02 (1, 1.1)
V_{MAX} for hepatic TCOH→TCA (mg/hour)	V_{MAX} TCOH	42 (0.77, 2200)	9.2 (5.5, 20)	1.83 (1.46, 3.43)	3.15 (2.3, 5.44)
K_M for hepatic TCOH→TCA (mg/L)	K_MTCOH	5 (0.23, 81)	2.2 (1.3, 4.5)	1.49 (1.25, 2.57)	2.58 (1.75, 4.5)
V_{MAX} for hepatic TCOH→TCOG (mg/hour)	V_{MAX} Gluc	720 (12, 50,000)	900 (340, 2,000)	1.83 (1.48, 3.5)	2.29 (1.84, 4.57)
K_M for hepatic TCOH→TCOG (mg/L)	K_MGluc	10 (0.53, 190)	130 (47, 290)	1.5 (1.25, 2.6)	1.58 (1.26, 3.69)
Rate constant for hepatic TCOH→other (/hour)	kMetTCOH	0.83 (0.035, 10)	0.25 (0.042, 0.7)	1.5 (1.26, 3)	5.13 (2.72, 16.7)
Rate constant for TCA plasma→urine (/hour)	kUrnTCA	0.26 (0.038, 4)	0.11 (0.083, 0.15)	1.48 (1.29, 2.29)	1.86 (1.58, 2.28)
Rate constant for hepatic TCA→other (/hour)	kMetTCA	0.19 (0.01, 2.6)	0.096 (0.038, 0.19)	1.48 (1.26, 2.57)	2.52 (1.79, 4.34)
Rate constant for TCOG liver→bile (/hour)	kBile	1.2 (0.059, 16)	2.5 (1.1, 6.9)	1.47 (1.25, 2.75)	1.56 (1.27, 3.21)
Lumped rate constant for TCOG bile→TCOH liver (/hour)	kEHR	0.074 (0.004, 1.4)	0.053 (0.033, 0.087)	1.52 (1.26, 2.64)	1.72 (1.35, 2.51)
Rate constant for TCOG→urine (/hour)	kUrnTCOG	2.9 (0.061, 260)	2.4 (0.83, 7)	1.75 (1.4, 3.31)	18.7 (11.6, 31.8)

Table 3-9. Prior and Posterior Uncertainty and Variability in Human PBPK Model Parameters

Parameter description	PBPK parameter	Prior population median: median (2.5%, 97.5%)	Posterior population median: median (2.5%, 97.5%)	Prior population GSD: median (2.5%, 97.5%)	Posterior population GSD: median (2.5%, 97.5%)
Rate constant for hepatic DCVG→DCVC (/hour)	kDCVG	0.044 (0.000063, 22)	2.5 (1.9, 3.4)	1.48 (1.25, 2.83)	1.51 (1.3, 1.86)
Lumped rate constant for DCVC→urinary NAcDCVC (/hour)	kNAT	0.00085 (0.000055, 0.041)	0.0001 (0.000047, 0.0007)	1.51 (1.25, 2.34)	1.47 (1.24, 2.48)
Rate constant for DCVC bioactivation (/hour)	kKidBioact	0.0022 (0.000095, 0.079)	0.023 (0.0062, 0.061)	1.51 (1.25, 2.57)	1.52 (1.25, 2.69)

Source: EPA 2011e

the liver metabolism in the EPA (2011e) model includes a GSH conjugation pathway as well as oxidation pathways, which compete for trichloroethylene as a substrate. The total rate of oxidation of trichloroethylene in liver (K_m, V_{max}) is split into fractions leading to TCA and trichloroethanol or to other oxidative pathways (e.g., leading to DCA but not via trichloroethanol). TCA formed in the liver is eliminated by conversion in the liver to downstream oxidative products (first order). Trichloroethanol undergoes three competing reactions in the liver consisting of conversion to TCA (K_m, V_{max}), trichloroethanol-glucuronide conjugate (K_m, V_{max}), or elimination to other products (e.g., DCA, first order). Trichloroethanol-glucuronide conjugate in liver is transferred to the gastrointestinal tract (first order) representing biliary secretion, from where it can be reabsorbed as trichloroethanol (first order) representing enterohepatic circulation. The hepatic GSH pathway leads to formation of DCVC from DCVG in liver. Activation of DCVC is assumed to occur in kidney, but not in liver. The hepatic oxidation products, TCA, trichloroethanol, and trichloroethanol-glucuronide conjugate, enter systemic blood and undergo flow-limited distribution to liver and to a lumped tissue compartment representing tissues other than liver (body). Urinary metabolites include TCA transferred from plasma (first order), trichloroethanol-glucuronide conjugate transferred from the lumped body compartment (first order), and NAcDCVC transferred after formation in kidney (first order).

Validation of the Model. Parameter values for the EPA (2011e) model were estimated by applying a hierarchical Bayesian approach (Markov Chain Monte Carlo, MCMC). Initial (*prior*) central estimates (median) and variance (geometric standard deviation) were made for each parameter. These estimates represent initial expectations of variability in each parameter value, based on data applied to the estimate, or scientific judgment, if no data were available. Prior estimates were updated by applying MCMC using data from approximately 30 rodent studies and 8 human studies to direct the Markov chain towards convergence with observations (e.g., a distribution of parameter values that yield distributions of model predictions in agreement with observations). In MCMC, a Markov chain is produced in which each step of the chain consists of repeated (e.g., n=1,000) random draws from each parameter distribution. Each draw from all parameters yields a single set of model predictions of observations (e.g., blood TCA concentration, urinary NAcDCVC). Each step in the chain (n draws) yields a distribution for each prediction (e.g., n=1,000). The distributions of model predictions are compared to observations available for each prediction. Based on acceptance or rejection criteria (i.e., whether or not the new predictions improve agreement with observations), the randomly drawn parameter values are accepted or rejected. If accepted, they establish the prior distributions for the next step in the Markov chain. The process is repeated many times (e.g., n=100,000) until the Markov chain achieves a stable probability of predicting observations (known as *convergence*). The resulting distributions of parameter values are referred to as

posterior distributions and represent estimates of the distributions of parameter values in the population of subjects consistent with measurement error and variability within the population and other unspecified sources of error in the model. The MCMC is repeated several times to evaluate stability of the outcomes.

Some model parameters were allometrically scaled across species using standard scaling assumptions (e.g., volumes, BW^1, first order rates, $BW^{-0.25}$, whole body flows V_{max}, $BW^{0.75}$). However, because these standard scaling factors are only approximations and because data were available for rats, mice, and humans, the scaled parameter values were also updated in a sequential MCMC analyses to account for residual error not reduced by standard allometric scaling assumptions (EPA 2011e). The sequence began with the MCMC analysis of the mouse model. Posterior distributions of the parameters to be scaled then served, along with a "scaling" error term, as priors for the MCMC analysis of the rat model. Posterior distributions for scaled parameters for the mouse and rat were combined and, with an additional error term, used as priors for the MCMC of the human model.

EPA (2011e) utilized approximately 30 data sets from rodent studies and 8 data sets from human studies to estimate posterior distributions for parameter values. The resulting calibrated model, with parameter values assigned from the posterior distributions, was evaluated against a validation set consisting of six data sets from rodent studies and 10 human studies, not used in the calibration. A complete list of data sets used in calibration and validation analyses is provided in Tables 3-10 and 3-11. Rodent data included oral gavage, intravenous, and inhalation studies of rats (predominantly) and mice. Human studies were all inhalation exposures.

Predictions of the calibrated model were compared at two levels. The first level was a comparison of model predictions of posterior parameter distributions derived for subjects representing specific observation data sets with the observation from the same data sets (i.e., predictions based on calibration with data set *i* compared to observations in data set *i*). Since these data sets were used to establish the posterior parameter distributions, as expected, posterior parameter distributions achieved good agreement when compared to data used in the calibration (i.e., in general, residuals were <2). This comparison confirmed success of the calibration. The second level was a validation of the calibrated model in which population posterior distributions were compared to observations that were not used to inform the MCMC calibration, using the 95% CI on predictions as a metric for evaluating agreement with observation (i.e., whether or not observations fell within the 95% CI of predictions). This validation analysis was possible only for the rat and human models; all available data were needed and used in the calibration of the mouse model. In general, the rat model predicted observations not included in calibration of the rat

Table 3-10. Rodent Studies with Pharmacokinetic Data Considered for Analysis

Reference	Species (strain)	Sex	TCE exposures	Other exposures	Calibration	Validation	Not used	Comments
Mouse studies								
Abbas et al. 1996	Mouse (B6C3F1)	M	–	CH intra-venous			√	CH not in model
Abbas and Fisher 1997	Mouse (B6C3F1)	M	Oral (corn oil)	–	√[a]			
Abbas et al. 1997	Mouse (B6C3F1)	M	–	TCOH, TCA intra-venous	√			
Barton et al. 1999	Mouse (B6C3F1)	M	–	DCA intra-venous and oral (aqueous)			√	DCA not in model
Birner et al. 1993	Mouse (NMRI)	M+F	Gavage	–			√	Only urine concentrations available, not amount
Fisher and Allen 1993	Mouse (B6C3F1)	M+F	Gavage (corn oil)	–	√			
Fisher et al. 1991	Mouse (B6C3F1)	M+F	Inhalation	–	√[a]			
Green and Prout 1985	Mouse (B6C3F1)	M	Gavage (corn oil)	TCA intra-venous	√			
Greenberg et al. 1999	Mouse (B6C3F1)	M	Inhalation	–	√[a]			
Larson and Bull 1992a	Mouse (B6C3F1)	M	–	DCA, TCA oral (aqueous)	√			Only data on TCA dosing was used, since DCA is not in the model
Larson and Bull 1992b	Mouse (B6C3F1)	M	Oral (aqueous)	–	√			
Merdink et al. 1998	Mouse (B6C3F1)	M	intra-venous	CH intra-venous	√			Only data on TCE dosing was used, since CH is not in the model
Prout et al. 1985	Mouse (B6C3F1, Swiss)	M	Gavage (corn oil)	–	√[a]			
Templin et al. 1993	Mouse (B6C3F1)	M	Oral (aqueous)	TCA oral	√[a]			

Table 3-10. Rodent Studies with Pharmacokinetic Data Considered for Analysis

Reference	Species (strain)	Sex	TCE exposures	Other exposures	Calibration	Validation	Not used	Comments
Rat studies								
Andersen et al. 1980	Rat (F344)	M	Inhalation	–		√[a]		
Barton et al. 1995	Rat (Sprague-Dawley)	M	Inhalation	–			√	Initial chamber concentrations unavailable, so not used
Bernauer et al. 1996	Rat (Wistar)	M	Inhalation	–	√[a]			
Birner et al. 1993	Rat (Wistar, F344)	M+F	Gavage (ns)	–			√	Only urine concentrations available, not amount
Birner et al. 1997	Rat (Wistar)	M+F	–	DCVC intra-venous			√	Single dose, route does not recapitulate how DCVC is formed from TCE, excreted NAcDCVC ~100-fold greater than that from relevant TCE exposures (Bernauer et al. 1996)
Bruckner et al. unpublished	Rat (Sprague-Dawley)	M	Inhalation	–		√		Not published, so not used for calibration; similar to Keys et al. (2003) data.
Dallas et al. 1991	Rat (Sprague-Dawley)	M	Inhalation	–	√			
D'Souza et al. 1985	Rat (Sprague-Dawley)	M	Intra-venous, oral (aqueous)	–			√	Only TCE blood measurements, and ≥10-fold greater than other similar studies
Fisher et al. 1989	Rat (F344)	F	Inhalation	–	√			
Green and Prout 1985	Rat (Osborne-Mendel)	M	Gavage (corn oil)	TCA gavage (aqueous)	√			

Table 3-10. Rodent Studies with Pharmacokinetic Data Considered for Analysis

Reference	Species (strain)	Sex	TCE exposures	Other exposures	Calibration	Validation	Not used	Comments
Hissink et al. 2002	Rat (Wistar)	M	Gavage (corn oil), intra-venous	–	√			
Jakobson et al. 1986	Rat (Sprague-Dawley)	F	Inhalation	Various pre-treatments (oral)		√		Pretreatments not included; only blood TCE data available
Kaneko et al. 1994	Rat (Wistar)	M	Inhalation	Ethanol pre-treatment (oral)	√			Pretreatments not included
Keys et al. 2003	Rat (Sprague-Dawley)	M	Inhalation, oral (aqueous), intra-arterial	–	√			
Kimmerle and Eben 1973a	Rat (Wistar)	M	Inhalation	–	√			
Larson and Bull 1992a	Rat (F344)	M	–	DCA, TCA oral (aqueous)	√			Only TCA dosing data used, since DCA is not in the model
Larson and Bull 1992b	Rat (Sprague-Dawley)	M	Oral (aqueous)	–	√[a]			
Lash et al. 2006	Rat (F344)	M+F	Gavage (corn oil)	–			√	Highly inconsistent with other studies
Lee et al. 1996	Rat (Sprague-Dawley)	M	Arterial, venous, portal, stomach injections	–		√		Only blood TCE data available
Lee et al. 2000a; 2000b	Rat (Sprague-Dawley)	M	Stomach injection, intra-venous, intra-perivenous	p-nitro-phenol pre-treatment (intra-arterial)	√	√		Pretreatments not included; only experiments with blood and liver data used for calibration
Merdink et al. 1999	Rat (F344)	M	–	CH, TCOH intra-venous	√			TCOH dosing used; CH not in model
Poet et al. 2000	Rat (F344)	M	Dermal	–			√	Dermal exposure not in model

Table 3-10. Rodent Studies with Pharmacokinetic Data Considered for Analysis

Reference	Species (strain)	Sex	TCE exposures	Other exposures	Calibration	Validation	Not used	Comments
Prout et al. 1985	Rat (Osborne-Mendel, Wistar)	M	Gavage (corn oil)	–	√[a]			
Saghir and Schultz 2002	Rat (F344)	M	–	DCA intra-venous, oral (aqueous)			√	DCA not in model
Simmons et al. 2002	Rat (Long-Evans)	M	Inhalation	–	√			
Stenner et al. 1997	Rat (F344)	M	intra-duodenal	TCOH, TCA intra-venous	√			
Templin et al. 1995b	Rat (F344)	M	Oral (aqueous)	–	√[a]			
Thrall and Poet 2000	Rat (F344)	M	intra-venous, intra-peritoneal	with toluene			√	Only exhaled breath data available from intravenous study; intra-peritoneal dosing not in model
Yu et al. 2000	Rat (F344)	M	–	TCA intra-venous	√			

[a]Part or all of the data in the study was used for calibration in Hack et al. (2006).

CH = chloral hydrate; DCA = dichloroacetic acid; DCVC = dichlorovinyl cysteine; F = female; M = male; NAcDCVC = N-acetyl-S-(dichlorovinyl)-L-cysteine; ns = not specified; TCA = trichloroacetic acid; TCE = trichloroethylene; TCOH = trichloroethanol

Source: EPA 2011e

Table 3-11. Human Studies with Pharmacokinetic Data Considered for Analysis

Reference	Species (number of individuals)	Sex	TCE exposures	Other exposures	Calibration	Validation	Not used	Comments
Bartonicek 1962	Human (n=8)	M+F	Inhalation	–		√		Sparse data, so not included for calibration to conserve computational resources
Bernauer et al. 1996	Human	M	Inhalation	–	√[a]			Grouped data, but unique in that includes NAcDCVC urine data
Bloemen et al. 2001	Human (n=4)	M	Inhalation	–		√		Sparse data, so not included for calibration to conserve computational resources
Chiu et al. 2007	Human (n=6)	M	Inhalation	–	√			
Ertle et al. 1972	Human	M	Inhalation	CH oral			√	Very similar to Muller et al. (1975) data
Fernandez et al. 1977	Human	M	Inhalation	–		√		
Fisher et al. 1998	Human (n=17)	M+F	Inhalation	–	√[a]			
Kimmerle and Eben 1973b	Human (n=12)	M+F	Inhalation	–	√			
Lapare et al. 1995	Human (n=4)	M+F	Inhalation	–		√[b]		Complex exposure patterns, and only grouped data available for urine, so used for validation
Lash et al. 1999b	Human	M+F	Inhalation	–	√			Grouped only, but unique in that DCVG blood data available (same individuals as Fisher et al. [1998])
Monster et al. 1976	Human (n=4)	M	Inhalation	–	√[b]			Experiments with exercise not included

Table 3-11. Human Studies with Pharmacokinetic Data Considered for Analysis

Reference	Species (number of individuals)	Sex	TCE exposures	Other exposures	Calibration	Validation	Not used	Comments
Monster et al. 1979	Human	M	Inhalation	–		√[a]		Grouped data only
Muller et al. 1972	Human	NS	Inhalation	–			√	Same data also included in Muller et al. (1975)
Muller et al. 1974	Human	M	Inhalation	CH, TCA, TCOH oral	√	√[a]		TCA and TCOH dosing data used for calibration, since it is rare to have metabolite dosing data; TCE dosing data used for validation, since only grouped data available; CH not in model
Muller et al. 1975	Human	M	Inhalation	Ethanol oral		√[a]		Grouped data only
Paykoc et al. 1945	Human (n=3)	NS	--	TCA intra-venous	√			
Poet et al. 2000	Human	M+F	Dermal	–				Dermal exposure not in model
Sato et al. 1977	Human	M	Inhalation	–		√		
Stewart et al. 1970	Human	NS	Inhalation	–		√[a]		
Triebig et al. 1976	Human	NS	Inhalation	–		√[a]		
Vesterberg and Astrand 1976	Human	M	Inhalation	–			√	All experiments included exercise, so were not included

[a]Part or all of the data in the study was used for calibration in Hack et al. (2006).
[b]Grouped data from this study was used for calibration in Hack et al. (2006), but individual data were used here.

CH = chloral hydrate; DCVG = S-dichlorovinyl glutathione; F = female; M = male; NAcDCVC = N-acetyl-S-(dichlorovinyl)-L-cysteine; NS = not specified; TCA = trichloroacetic acid; TCE = trichloroethylene; TCOH = trichloroethanol

Source: EPA 2011e

model, with the observations of trichloroethylene concentrations in blood and tissues (liver, gastrointestinal tract, skeletal muscle, venous blood) within the 95% CI of predictions (U.S. EPA, 2011e). The only exception reported was an under-prediction of observed kidney levels of trichloroethylene during an inhalation exposure to 500 ppm trichloroethylene, although post-exposure levels were accurately predicted. The human model also performed well against observations not included in model calibration, although observations were limited to trichloroethylene concentrations in blood and exhaled air and TCA and trichloroethanol in blood and urine. The human model showed a tendency (not in all studies) to over-predict trichloroethylene concentrations in exhaled air.

Risk Assessment. The EPA (2011e) applied the trichloroethylene model for extrapolating external dose response relationships for cancer and noncancer end points observed in rats to humans in derivation of a chronic Reference Concentration (RfC), chronic Reference Dose (RfD), inhalation cancer unit risk, and oral cancer slope factor for trichloroethylene. Candidate inhalation exposure-response and oral dose-response relationships and corresponding BMDLs or NOAELs and LOAELs were derived from rodent bioassay data. For each candidate critical effect, internal dose metrics were selected that would be expected to relate to each response. The rodent PBPK models were used to predict internal doses that corresponded to the inhalation exposures or oral doses used in the rodent bioassay. The median of the distribution of predicted internal doses was selected to represent the typical rodent internal dose. A point of departure for internal dose (idPOD) was derived from internal dose-response analyses (e.g., BMD analysis or selection of NOAELs and/or LOAELs). The rodent idPOD was extrapolated to a human equivalent concentration (HEC, mg/m^3) for inhalation exposures or human equivalent dose (HED, mg/kg/day) for oral exposures, where the HEC and HED represent the continuous inhalation or oral exposure, respectively, corresponding to the idPOD in the human. Interspecies extrapolation was based on application of the human PBPK model, using posterior parameter distributions for humans to derive human internal dose distributions for a range of inhalation or oral exposures. The internal dose distributions at each exposure level were based on 500 random draws from the posterior parameter distributions (represented a sample of n=500) from the human population. The posterior parameter distributions in the human model represent predicted population variability in parameter values. Therefore, the model predicts distributions of internal doses corresponding to a given human exposure that reflect population variability in toxicokinetics of trichloroethylene. The median of this distribution was assumed to represent the typical internal dose corresponding to a given exposure, while the 99th percentile was assumed to represent a sensitive subpopulation. Based on the predicted median and 99th percentile internal doses, HECs or HEDs representing the typical internal dose and (HEC_{50}, HED_{50}) and sensitive subpopulation (HEC_{99}, HEC_{99}) were derived. The model-based derivation of the

99th percentile values was used as a rationale for eliminating the need for application of uncertainty factors to adjust the HEC_{99} or HED_{99} to account for interspecies toxicokinetics variability ($10^{0.5}$) and for human variability in toxicokinetics ($10^{0.5}$). Uncertainty factors applied to the HEC_{99} or HED_{99} were $10^{0.5}$ to account for possible interspecies variability in toxicodynamics, and $10^{0.5}$ to account for possible human population variability in toxicodynamics.

Several internal dose metrics were considered in analyses supporting the derivation of the RfC, RfD, inhalation cancer unit risk, and oral cancer slope factor (EPA 2011e). These included the AUC for trichloroethylene, TCA, or trichloroethanol concentrations in blood, amounts of trichloroethylene metabolized (to GSH conjugates, oxidized) per unit body weight of metabolizing tissue weight (liver or kidney), and amount of DCVC activated per unit of body weight or kidney weight. The RfC was ultimately based on production of developmental heart defects and immunological effects as critical effects, supported by dose-response relationships for nephropathy. The internal dose metric selected to represent the developmental heart effects was the total amount of trichloroethylene metabolized through oxidative pathways in all metabolizing tissues per unit of body weight. This internal dose metric is considered appropriate because results of several studies demonstrate that selected oxidative trichloroethylene (TCA or DCA) induce cardiac malformations. The internal dose metric selected to represent the immunological effects was the total amount of trichloroethylene metabolized through all pathways in all metabolizing tissues per unit of body weight due to a lack of information on the role of metabolites or mode of action for trichloroethylene-induced immunological effects. Internal dose metrics used to represent kidney effects were the amount of DCVC activated per unit of body weight or the amount of trichloroethylene conjugated with GSH per unit of body weight, based on the conclusion that trichloroethylene-induced kidney toxicity is caused primarily by GSH conjugation metabolites (particularly DCVC). The RfD was also based on developmental heart defects and immunological effects as critical effects, supported by nephropathy. Internal dose metrics selected to represent these effects were the same as those used in the derivation of the RfC. A variety of internal dose metrics were evaluated in support for the derivation of the inhalation cancer unit risk and oral cancer slope factor, which depended on the tissue location of the cancers observed (e.g., lung, liver, kidney, or other tissues).

Target Tissues. The trichloroethylene model (EPA 2011e) was calibrated to predict blood trichloroethylene, TCA, and trichloroethanol kinetics; rates of metabolism of trichloroethylene in lung, liver, and kidney; and excretion of trichloroethylene metabolites following inhalation or oral exposures to trichloroethylene. As noted above, the model has been used to predict various internal dose metrics of trichloroethylene exposure in rats and humans (EPA 2011e). These include the AUC for

trichloroethylene, TCA, or trichloroethanol concentrations in blood; amounts of trichloroethylene metabolized (to GSH conjugates, oxidized) formed per unit body weight or metabolizing tissue weight (liver or kidney); and amount of DCVC activated per unit of body weight or kidney weight.

Interspecies Extrapolation. As described above, models simulating toxicokinetics in mice, rats, and humans have been used in interspecies extrapolation of external-internal dose response relationships (EPA 2011e). Models for the above species were developed by a combination of allometric scaling across species and optimization of scaled model parameters (metabolism V_{max} and rate constants) using hierarchical Bayesian analyses. The scaled rat and human models have been evaluated against independent observations not used to estimate model parameter values (EPA 2011e).

Interroute Extrapolation. The trichloroethylene model (EPA 2011e) as it is currently configured simulates trichloroethylene kinetics associated with inhalation, oral, and intravenous dosing. Simulation of other potential routes of exposure (e.g., dermal) would require development of models for the absorption of trichloroethylene deposited on the skin. EPA (2011e) used the PBPK model to perform oral-to-inhalation extrapolation in deriving a chronic RfC for trichloroethylene based on internal dose. EPA (2011e) used the human model to extrapolate from an inhalation cancer unit risk to an oral cancer slope factor. The basis of the inhalation cancer unit risk was epidemiological evidence of cancers in humans exposed to trichloroethylene along with supporting evidence from rodent bioassays. The interroute extrapolation was based on the internal dose metrics considered to be related to cancer, the amount of DCVC activated in kidney per unit of body weight, or the total amount of trichloroethylene metabolized per unit of body weight.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

Absorption. Trichloroethylene, like other volatile hydrocarbons, disrupts the cellular phospholipid membrane, thereby allowing for easy absorption. Trichloroethylene-induced changes in fatty acid composition in rat brain and liver may influence its ability to cross affected membranes (Okamoto and Shiwaku 1994). However, at concentrations found in most occupational and environmental settings, diffusion is the mechanism whereby small uncharged lipophilic molecules such as trichloroethylene are absorbed through the skin.

Distribution. Once inside the body, trichloroethylene is readily absorbed into and distributed throughout the body via the circulatory system. The amount that is not absorbed initially on inhalation is expired unchanged (see Section 3.3.1.1). Absorption from the gastrointestinal tract often leads to a first pass through the liver, where toxic and nontoxic metabolites can form (see Section 3.4.3). Trichloroethylene's metabolites may bind to, or form adducts with, blood proteins; the metabolite glyoxylate becomes incorporated into amino acids (Stevens et al. 1992).

Storage. The primary storage area for trichloroethylene in the body is the adipose tissue, as would be expected based on the lipophilicity of the compound (Fernandez et al. 1977; Monster et al. 1979).

Excretion. Much of the initially inhaled trichloroethylene is expired unchanged. Trichloroethylene has been detected in the breath of people exposed orally and dermally as well. Once absorbed, trichloroethylene is rapidly metabolized by well-characterized pathways of xenobiotic metabolism, such as the cytochrome P450 oxidation and GSH conjugation pathways, and many metabolic products are then excreted, mainly in the urine. No evidence exists for reabsorption from the kidney, although a decreased rate of excretion may be observed in persons with extra fat tissue because of trichloroethylene's tendency as a lipophilic compound to sequester in fat. The urinary excretion of TCA is slower than that of other trichloroethylene metabolites because TCA is very tightly and extensively bound to plasma proteins (Monster et al. 1976; Sato et al. 1977).

Route Dependent Toxicity. The toxicity of trichloroethylene does not seem to be heavily dependent upon its route of entry. Inhalation and ingestion are the primary exposure routes. As discussed in the *Health Effects by Route of Exposure* sections of this profile, health effects are similar across these routes. Toxic effects from dermal exposure are generally confined to the skin, although broad systemic effects can be induced under conditions of high exposure (Bauer and Rabens 1974). Attributing such effects solely to dermal exposure, however, is difficult because inhalation exposure is often a factor in these cases as well.

3.5.2 Mechanisms of Toxicity

Effects of Metabolism on Toxicity. For trichloroethylene, the mechanisms of target organ toxicity are closely related to its metabolism. Therefore, some of the information regarding the relationship between metabolism and toxicity is presented in the following section on Target Organ Toxicity.

An example is the rate by which the oxidative metabolism of trichloroethylene produces carcinogenic byproducts such as TCA. B6C3F1 mice, which are far more prone to trichloroethylene-induced liver cancer, exhibit rapid metabolism of inhaled trichloroethylene, while F344 rats and humans, which are less prone to such cancer, exhibit limited rates of metabolism (Abelson 1993; Stott et al. 1982). Larson and Bull (1992b) found that peak blood concentrations of TCA and trichloroethanol following a single oral dose of trichloroethylene (197–3,022 mg/kg) were much greater in mice than in rats, whereas the residence time of trichloroethylene (and therefore TCA and trichloroethanol) was greater in rats (a consequence of the slower rate of trichloroethylene metabolism in rats relative to mice). The net metabolism of trichloroethylene to TCA and trichloroethanol is similar in rats and mice. However, the initial rate of metabolism is higher in mice, especially as the trichloroethylene dose is increased; thus, the blood concentration of TCA is higher in mice. Since the target organs of mice are exposed to higher concentrations of potentially mutagenic/carcinogenic compounds, they are more susceptible to hepatotoxicity and hepatocarcinogenicity (Stott et al. 1982; Templin et al. 1993).

Isomers of DCVC, a product of trichloroethylene conjugation with GSH, are mutagenic in the *in vitro* Ames assay (Commandeur et al. 1991; Dekant et al. 1986c; Irving and Elfarra 2013). Additional information is provided in the Target Organ Toxicity section, under Renal Effects.

Metabolic differences between humans and other animals may account for some of the interspecies differences in specific organ toxicity of trichloroethylene (see below). Among humans, gender differences due mainly to the effects of body fat content (generally higher in women) on trichloroethylene absorption are expected based on PBPK modeling (see Section 3.4.5).

Target Organ Toxicity. Based on effects reported in humans and/or animals, the primary targets for trichloroethylene toxicity appear to be the nervous system, liver, kidney, immune system, male reproductive system, and developing fetus.

Neurological Effects. Although mechanistic studies of trichloroethylene neurotoxicity have been performed, the mechanisms for this toxicity are not well established (EPA 2011e; NRC 2006). Trichloroethylene and some of its metabolites such as chloral hydrate are central nervous system depressants and this property, mediated through effects on inhibitory neuronal receptors, may account for some of the behavioral changes associated with trichloroethylene exposure (EPA 2011e). Oxidative stress may also contribute to trichloroethylene-induced abnormal motor abnormalities. In mice deficient in superoxide dismutase, motor activity was significantly depressed compared to mice with superoxide

dismutase (Otsuki et al. 2016). Although it has been suggested that changes in trigeminal nerve function may be due to dichloroacetylene, which is produced under non-biological conditions (high alkalinity or temperature) during volatilization of trichloroethylene, exposure to this chemical has not been identified or measured in epidemiologic studies. In addition, changes in trigeminal nerve function also have been reported in humans exposed orally (EPA 2011e), and changes in trigeminal nerve morphology have been reported in rats exposed orally (Barret et al. 1991, 1992). Oral exposures are not expected to involve exposure to dichloroacetylene. Dopamine neuron disruption, including degeneration of dopamine neurons in the substantia nigra, has been reported in animal studies (Gash et al. 2008; Guehl et al. 1999) and has been suggested as a potential mechanism for clinical psychomotor effects from trichloroethylene exposure (EPA 2011e). A possible mechanism of hearing impairment was hypothesized, by analogy to aromatic hydrocarbons such as toluene, to involve toxicity to supporting cells in the cochlea, which then alters structural elements, ultimately resulting in hair cell displacement and death (EPA 2011e). Another potential mechanism is blockade of neuronal nicotinic receptors on the auditory cells and changes in calcium transmission seen with toluene and speculated to be relevant to trichloroethylene (EPA 2011e). Pre- and postnatal exposure of male MRL+/+ mice to trichloroethylene resulted in altered glutathione redox homeostasis (indicating a more oxidized state) and dose-related increased levels of glutathione precursors within the hippocampus, alterations in plasma metabolites involved in transsulfuration and transmethylation pathways (indicating redox imbalance and altered methylation capacity), significantly increased levels of 3-nitrotyrosine (a biomarker of protein oxidative stress) in plasma and hippocampus, and significantly decreased expression of key neurotrophic factors (brain-derived neurotrophic factor, nerve growth factor, neurotropin-3) compared to controls (Blossom et al. 2012). These results indicate that trichloroethylene-mediated neurotoxicity following repeated exposure might include modulation of neurotropin gene expression in the hippocampus. Blossom et al. (2013) demonstrated that postnatal oral exposure of male MRL+/+ mice to trichloroethylene resulted in effects within the cerebellum that included altered homeostasis, increased cysteinylglycine, increased 3-nitrotyrosine (a marker of oxidative protein damage), decreased methionine, and decreased global DNA methylation; the trichloroethylene-treated mice exhibited increased locomotor and exploratory activity. The study authors postulated that postnatal exposure to trichloroethylene resulted in key metabolic changes in the cerebellum that may contribute to global DNA methylation deficits and altered behavior.

Hepatic Effects. The oxidative metabolites of trichloroethylene, particularly chloral hydrate, TCA, and DCA, are thought to contribute to liver toxicity in humans and animals and to liver cancer in mice (EPA 2011e; NRC 2006). This conclusion is based on the studies in animals showing the potentiation of liver effects by pretreatment with cytochrome P450 inducers and the similarity of effects, such as increased

liver weight, peroxisome proliferation, and liver cancer, produced by trichloroethylene and these metabolites. *In vitro* exposure of human hepatic L-02 cells to trichloroethylene was performed to provide insight into possible mechanisms of trichloroethylene hepatotoxicity. Yang et al. (2012) reported decreased cell viability, increased apoptosis and elevated inhibitor 2 of protein phosphatase 2A (I2PP2A) mRNA and protein levels, and reduced PP2A activity; lentivirus-mediated I2PP2A knockdown partially reversed the effect on cell viability, apoptosis, and PP2A activity, and prevented caspase-3-mediated activation. The results indicated that I2PP2A may play a crucial role in mediating trichloroethylene hepatotoxicity. Hong et al. (2012) performed a proteomic analysis to identify the proteins that interact with I2PP2A (also known as SET/TAF-1α) and found that trichloroethylene significantly upregulated two SET/TAF-1α-binding proteins (elongation factors eEF1A1 and eEF1A2) and two isoforms of SET, as well as induced a redistribution of SET from nucleus to cytoplasm and eEF1A1 from cytoplasm to nucleus. Xu et al. (2012) observed significantly increased transcript levels of hepatic metabolic enzyme genes (CYP1A2, CYP3A4, CYP2E1) and apoptosis genes (BAD, BAX), suggesting that trichloroethylene-induced alteration of mRNA expression of hepatic metabolic enzyme genes and apoptosis genes may be involved in trichloroethylene hepatotoxicity.

Several potential modes of action for trichloroethylene-induced liver tumors in animals have been proposed. One hypothesis is a mutagenic mode of action in which key events include the oxidative metabolism of trichloroethylene in the liver to chloral hydrate or some other oxidative metabolite, resulting in mutations, DNA damage, and/or micronuclei induction (EPA 2011e). Another proposed mode of action suggests that trichloroethylene's metabolite TCA activates the peroxisome proliferator activated receptor alpha (PPARα) in the liver, which causes alterations in cell proliferation and apoptosis, and clonal expansion of initiated cells (EPA 2011e). Additional proposed hypotheses for modes of action for liver cancer include:

- Polyploidization: Trichloroethylene and other substances that contribute to liver tumor induction also cause polyploidy in hepatocytes.

- Changes in glycogen storage: The trichloroethylene metabolite, DCA, has been demonstrated to cause accumulation of glycogen in hepatocytes of mice (Kato-Weinstein et al. 1998). In humans, glycogenesis due to glycogen storage disease or poorly controlled diabetes has been associated with increased risk of liver cancer (Adami et al. 1996; La Vecchia et al. 1994; Rake et al. 2002; Wideroff et al. 1997).

- Inhibition of glutathione-S-transferase zeta (GSTz): Studies in rodents have demonstrated that the trichloroethylene metabolite, DCA (a proximate hepatotoxicant), inhibits GSTz1-1 (an enzyme that catalyzes the glutathione-dependent conversion of DCA itself to glyoxylate), thus resulting in a longer biological half-life for DCA (Guo et al. 2006; Schultz et al. 2002).

- Oxidative stress and resultant DNA damage.
- Changes in gene expression, particularly DNA methylation induced by reactive metabolites of trichloroethylene. For example, altered expression of cell cycle regulating genes (p53, p21, bax and bcl-2) was observed in workers exposed to trichloroethylene (Varshney et al. 2015).
- A study in B6C3F1 mice exposed to oral tetrachloroethylene reported a dose-related increase in the number of transcriptomes (sum of messenger RNA molecules) in the liver (Zhou et al. 2017). Results indicate that epigenetic mechanisms may be involved in the development of trichloroethylene-induced toxicity.
- Cytotoxicity and subsequent induction of reparative hyperplasia.

EPA (2011e), however, concluded that the data are inadequate to support the conclusion that any of these hypotheses are operant, and that therefore, the mode of action for trichloroethylene induction of liver tumors is unknown. The human relevance of trichloroethylene-induced hepatocarcinogenicity in mice is questionable based on the following observations. Relatively high trichloroethylene exposure levels were required to induce hepatocarcinogenicity in mice and trichloroethylene did not induce liver tumors in rats. Mice metabolize trichloroethylene more rapidly than rats, and metabolism of trichloroethylene in humans is thought to be more comparable to that of rats than mice. A major trichloroethylene metabolite, trichloroacetate, induces liver tumors in mice via a PPARα mode of action as demonstrated by the lack of trichloroethylene-induced liver tumors in PPARα-null mice, a mode of action that is of questionable relevance to humans (for more in-depth mode of action discussions regarding trichloroethylene and liver cancer, see Corton 2008; EPA 2011e, Klaunig et al. 2003; NRC 2009).

Renal Effects. The GSH-dependent metabolites of trichloroethylene, DCVC, and related GSH conjugation metabolites, are considered to be the active agents of trichloroethylene renal toxicity and carcinogenicity (EPA 2011e). *In vivo* and *in vitro* studies show that 1,2-DCVC causes renal effects that are similar to those of trichloroethylene, and that it is formed in sufficient amounts after trichloroethylene exposure to account for these effects. EPA (2011e) concluded that renal carcinogenicity occurs through a mutagenic mode of action mediated by the GSH-conjugation metabolites of trichloroethylene, predominantly DCVC. This conclusion is based on evidence that these metabolites are genotoxic, including *in vivo* evidence of renal-specific genotoxicity from exposure to trichloroethylene or 1,2-DCVC. The mode of action includes cytotoxicity resulting in compensatory cellular proliferation, also due to DCVC. Again, the evidence was primarily from studies with 1,2-DCVC. The combination of these mechanisms, with increased rates of mutation and regenerative proliferation enhancing cell survival or clonal expansion is considered biologically plausible, but without experimental support.

The plasma kallikrein-kinin system may also have a role in trichloroethylene-induced renal effects. In mice sensitized with trichloroethylene, inflammatory cell infiltration was observed. In addition, immunochemistry evaluation of the proximal tubule showed increase expression of bradykinin and plasma kallikrein (Wang et al. 2016). Cytokine deposition was observed in the proximal tubule of trichloroethylene-sensitized guinea pigs, suggesting that immune dysfunction may be involved in the development of renal damage (Yu et al. 2017). Oxidative stress may be important in trichloroethylene-induced renal damage and altered renal function. In rats administered intraperitoneal injections of trichloroethylene (200–2,000 mg/kg/day) for 7 days, vitamin E, an antioxidant, significantly reduced toxicity (Heydari et al. 2017).

Immunological Effects. The mechanism of action for immunological effects, including autoimmune disease and lymphoma, is not known (EPA 2011e). Some mechanistic studies have focused on oxidative stress as a potential mechanism for induction of immune effects (Khan et al. 2001; Wang et al. 2008, 2007b). Studies in mice susceptible to autoimmune disease indicate that trichloroethylene oxidative metabolites such as chloral (also known as trichloroacetaldehyde) or dichloroacetyl chloride may be responsible, at least in part, for activating T-cells or altering T-cell regulation and survival associated with polyclonal disease (Blossom and Gilbert 2006; Blossom et al. 2007; Cai et al. 2006; Gilbert et al. 2004). Results of a local lymph node assay in mice suggest that transforming growth factor-β activated kinase-1 may be involved in trichloroethylene-induced contact hypersensitivity (Yao et al. 2016).

Seo et al. (2012) reported trichloroethylene-induced enhancement of histamine release from antigen-stimulated mouse bone marrow-derived mast cells and noted that this effect was not produced by major trichloroethylene metabolites, TCA or chloral. Blossom et al. (2010) found that the trichloroethylene metabolite, trichloroacetaldehyde hydrate, promoted increased reactive oxygen species associated with alterations in the expression of genes involved in differentiation of thymocytes from autoimmune-prone MRL+/+ and non-autoimmune-prone mice.

A group of 28 trichloroethylene-induced hypersensitivity dermatitis patients exhibited significantly higher levels of serum interleukins (IL-1β, IL-6, IL-8) and tumor necrosis factor-α than trichloroethylene-exposed workers without hypersensitivity dermatitis (n=22) or non-exposed controls (n=22) (Jia et al. 2012). *In vitro* assessment of cytokine expression in the keratinocyte cell line (HaCaT) exposed to trichloroethanol or TCA (metabolites of trichloroethylene) revealed that trichloroethanol (but not trichloroacetate) increased levels of IL-1α and IL-6 in a dose-dependent manner and activated the nuclear factor kappa B pathway. Bay 11-7082 (a nuclear factor kappa B inhibitor) significantly attenuated the

trichloroethanol-induced production of IL-6, but not IL-1α (Jia et al. 2012). These results suggest that trichloroethanol-induced IL-6 expression via activation of the nuclear factor kappa B pathway in HaCaT cells may be involved in trichloroethylene-induced skin hypersensitivity.

Male Reproductive Effects. The evidence suggests that trichloroethylene is metabolized in the male reproductive tract, primarily in the epididymal epithelium, but also in testicular Leydig cells, by CYP2E1 to chloral, trichloroethanol, and TCA (Forkert et al. 2002, 2003). The finding of dichloroacetyl protein adducts in the epididymis and efferent ducts of rats administered trichloroethylene and of oxidized proteins on the surface of their spermatozoa suggested that male reproductive toxicity was initiated by metabolic activation of trichloroethylene to reactive metabolites (DuTeaux et al. 2003, 2004). The mechanism of male reproductive toxicity, however, is not clearly established.

Developmental Effects. A number of studies of the potential mechanisms for trichloroethylene-induced fetal cardiac defects have focused on disruptions in cardiac valve formation using chickens as a model. The use of an avian model is supported by the substantial concordance in the stages and events of cardiac valve formation between mammals and birds (NRC 2006). These studies demonstrated alterations in endothelial cushion development, which could be associated with defects in septal and valvular morphogenesis (e.g., Boyer et al. 2000; Mishima et al. 2006). The proposed mechanism is inhibition of endothelial separation and formation of mesenchymal cells (from which the septum and valves are formed). An additional study in bovine coronary endothelial cells (Ou et al. 2003) supported a mechanism of interference with the role of endothelial nitric oxide synthase in endothelial cell proliferation.

3.5.3 Animal-to-Human Extrapolations

PBPK models for trichloroethylene have evolved in complexity to address specific problems in toxicokinetics extrapolation (Chiu et al. 2009; EPA 2011e; Evans et al. 2009; Fisher 2000; Hack et al. 2006; Keys et al. 2003; Poet et al. 2000; Simmons et al. 2002; Thrall and Poet 2000). The most recent model (Chiu et al. 2009; Evans et al. 2009) was utilized by EPA (2011e) to derive chronic RfD and RfC values for trichloroethylene using animal-to-human and route-to-route (oral-to-inhalation) extrapolation. This model serves as basis for derivation of the intermediate- and chronic-duration oral and inhalation MRLs as well (see Section 2.3).

In the mouse, rat, and human, metabolism of trichloroethylene occurs via two major capacity-limited pathways: oxidation by CYP2E1 and conjugation with GSH. The GSH conjugation pathway results in production of reactive intermediates that are thought to contribute to trichloroethylene toxicity (see Section 3.5.2). Based on comparisons of predictions from the mouse, rat, and human PBPK models, humans are predicted to have a lower capacity to oxidize trichloroethylene via the CYP2E1 pathway and a higher capacity to conjugate trichloroethylene with GSH. As a result, a larger fraction of an absorbed dose of trichloroethylene is expected to be metabolized through the GSH conjugation pathway in humans compared to rodents (Chiu et al. 2009). This is predicted to result in a higher toxic potency of trichloroethylene in humans, based on external dose (or exposure). The PBPK models provide a basis for accounting for these differences in metabolism and generation of toxic reactive species by allowing the dose-response relationships to be derived based on internal dose metrics such as amount of metabolite(s) at any given external dose (EPA 2011e).

Species differences in elimination kinetics may also result in species differences in temporal profiles of trichloroethylene or its metabolites during repeated dosing. Rodents are predicted to have higher rates of elimination than humans based on allometric assumptions of scaling of metabolism to body size (Chiu et al. 2009). PBPK models provide a means for accounting for these differences.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Thomas and Colborn (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active

chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

Limited information is available regarding the potential for trichloroethylene to affect endocrine function. It is not likely that trichloroethylene would act as a hormonal agonist or antagonist because its chemical structure does not resemble endogenous hormones.

In occupational studies of men who used trichloroethylene to degrease electronic equipment, increasing years of exposure to trichloroethylene was associated with increased serum dehydroepiandrosterone sulphate and decreases in serum levels of testosterone, follicle-stimulating hormone, and sex-hormone binding globulin (Chia et al. 1997; Goh et al. 1998). Serum androstenedione, cortisol, and aldosterone levels were in normal ranges.

Significantly decreased serum testosterone (31–48% less than that of controls) and decreased testicular 17β-hydroxy steroid dehydrogenase were noted in rats exposed to trichloroethylene vapors at 376 ppm, 4 hours/day, 5 days/week for 12 or 24 weeks (Kumar et al. 2000a). No histopathological changes in the pituitary gland, adrenal glands, or pancreas were observed in rats exposed to 600 ppm trichloroethylene 7 hours/day, 5 days/week for 104 weeks (Maltoni et al. 1988).

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 most biological systems 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 adverse health effects from exposure to hazardous chemicals, but whether there is a difference depends on the chemical(s) (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to exposure-related 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 that are most sensitive to disruption from exposure to hazardous substances. Damage from exposure in one stage 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). Past literature has often described the fetus/infant as having an immature (developing) blood-brain barrier that is leaky and poorly intact (Costa et al. 2004). However, current evidence suggests that the blood-brain barrier is anatomically and physically intact at this stage of development, and the restrictive intracellular junctions that exist at the blood-CNS interface are fully formed, intact, and functionally effective (Saunders et al. 2008, 2012).

However, during development of the brain, there are differences between fetuses/infants and adults that are toxicologically important. These differences mainly involve variations in physiological transport systems that form during development (Ek et al. 2012). These transport mechanisms (influx and efflux) play an important role in the movement of amino acids and other vital substances across the blood-brain barrier in the developing brain; these transport mechanisms are far more active in the developing brain than in the adult. Because many drugs or potential toxins may be transported into the brain using these same transport mechanisms—the developing brain may be rendered more vulnerable than the adult.

Thus, concern regarding possible involvement of the blood-brain barrier with enhanced susceptibility of the developing brain to toxins is valid. It is important to note however, that this potential selective vulnerability of the developing brain is associated with essential normal physiological mechanisms; and not because of an absence or deficiency of anatomical/physical barrier mechanisms.

The presence of these unique transport systems in the developing brain of the fetus/infant is intriguing; whether these mechanisms provide protection for the developing brain or render it more vulnerable to toxic injury is an important toxicological question. Chemical exposure should be assessed on a case-by-case basis. Research continues into the function and structure of the blood-brain barrier in early life (Kearns et al. 2003; Saunders et al. 2012; Scheuplein et al. 2002).

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 given their low glomerular filtration rate and not having 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).

Intake from trichloroethylene-contaminated drinking water is expected to be greater in children than adults because children tend to drink more water on a per kg body weight basis than adults. Fan (1988) estimated that average doses to a 10-kg infant, a 22-kg child, and a 70-kg adult would be 0.3, 0.204, and 0.086 mg trichloroethylene/kg/day, respectively, from consumption of drinking water containing 3 ppm of trichloroethylene, and that trichloroethylene doses via dermal and inhalation routes from bathing or

showering in water containing 3 ppm of trichloroethylene would be greater in children than adults. Household dust and dirt are potential sources of greater potential dermal contact and ingestion exposure in small children. Trichloroethylene intake from the ambient air is expected to be greater in infants and children than adults because infants and children have increased ventilation rates per kg body weight and increased cardiac output per kg body weight (EPA 2008; NRC 2009; Snodgrass 1992). Following inhalation exposure, peak concentrations of trichloroethylene in the blood of lactating rat pups were higher than those in similarly-exposed adult rats (Rodriguez et al. 2007). Levels of enzymes that metabolize xenobiotics are lower in neonates than adults, an indication that neonates may exhibit a lesser degree of susceptibility to the adverse effects of reactive trichloroethylene metabolites. In apparent contrast, the observation that half-lives of chloral hydrate (a reactive metabolite of trichloroethylene) are 3–4 times longer in premature and full-term newborns than in young children (Reimche et al. 1989) suggests that infants may be more susceptible than older children and adults to the toxic effects of reactive trichloroethylene metabolites. Greater metabolic clearance of trichloroethylene and many other drugs in children 1–6 years old than in adults is apparently due to children's larger liver volume and higher blood flow rate (Murray et al. 1995), rather than higher CYP2E1 activity (Blanco et al. 2000).

Trichloroethylene is lipophilic and distributes to all body tissues (see Section 3.4.2). At comparable absorption levels, such lipophilic substances may become more concentrated in the fat of infants and small children due to their lower amounts of fat per kilogram body weight compared to adolescents and adults (NRC 1993). Nursing infants can be exposed to trichloroethylene via the breast milk; Fisher et al. (1990) modeled distribution of trichloroethylene and TCA in the nursing mother rat and pup. In the past, when trichloroethylene was administered to some pregnant mothers during childbirth, ratios of trichloroethylene in fetal:maternal blood ranged from 0.5 to 2 (Laham 1970), indicating that trichloroethylene could accumulate in the fetus. Trichloroethylene crosses the blood-brain barrier, and the extent of transfer could possibly be greater in young children, although trichloroethylene is expected to readily cross the blood-brain barrier in all age groups. Age-related differences in trichloroethylene metabolism could result in differences in susceptibility to trichloroethylene toxicity. One study in rats reported increased trichloroethylene metabolism in 3-week-old rat weanlings compared to 18-week-old adult rats (Nakajima et al. 1992b). However, age-related differences in trichloroethylene metabolism have not been demonstrated in humans.

As discussed in detail in Section 3.2, results of some epidemiological studies indicate that trichloroethylene in the drinking water, ambient air, or workplace environments may be associated with developmental effects such as increased rates of spontaneous abortion (Windham et al. 1991), congenital

heart defects (ATSDR 2006, 2008; Goldberg et al. 1990; Yauck et al. 2004), ocular and auditory defects and other central nervous system abnormalities (ATSDR 1999; Bove et al. 1995; Lagakos et al. 1986a; MDPH 1996; Narotsky et al. 1995; White et al. 1997), oral cleft (Bove et al. 1995; Lagakos et al. 1986a), neural tube defects (Bove et al. 1995), and choanal atresia (a rare respiratory disorder) and hypospadias/congenital chordee (MDPH 1996). Results of some animal studies indicate that trichloroethylene can cause cardiac malformations (Dawson et al. 1993; Johnson et al. 1998, 2003), decreases in litter size and perinatal survival (Manson et al. 1984; Narotsky and Kavlock 1995; Narotsky et al. 1995; NTP 1986), compromised postnatal immune function (Blossom and Doss 2007; Blossom et al. 2008; Peden-Adams et al. 2006), altered behavior (Fredriksson et al. 1993; NTP 1986; Taylor et al. 1985), and alterations in brain morphology and physiology (Isaacson and Taylor 1989; Noland-Gerbec et al. 1986). It should be noted that human and animal data do not suggest that trichloroethylene is teratogenic.

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).

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

Biological monitoring for exposure to trichloroethylene is possible by measuring levels of the parent compound or the metabolites in exhaled air, blood, or urine. However, it should be noted that metabolites of trichloroethylene may also come from other sources; they are not specific to trichloroethylene exposure alone. Biological monitoring for trichloroethylene exposure has been performed for occupational exposures as well as for the general population. Following inhalation exposure in humans, most (approximately 58%) of the retained dose of trichloroethylene is metabolized and excreted as metabolites in the urine (Monster et al. 1976). Only a small amount (10–11%) of the absorbed dose is exhaled as unchanged trichloroethylene through the lungs, and 2% of the dose is eliminated by the lungs as trichloroethanol. Correlations were found between levels of trichloroethylene in ambient air and levels of trichloroethylene in human breath (Kimmerle and Eben 1973b; Monster et al. 1979; Stewart et al. 1970, 1974b; Wallace 1986; Wallace et al. 1985). Thus, this exposure-excretion relationship supports the use of breath levels for the prediction of exposure levels.

Monitoring for exposure to trichloroethylene has been performed by measuring trichloroethylene and its principal metabolites (TCA, trichloroethanol, trichloroethanol glucuronide) in blood and urine (Csanády et al. 2010; Ertle et al. 1972; Ikeda et al. 1972; Imamura and Ikeda 1973; Imbriani et al. 2001; Kimmerle and Eben 1973b; Monster et al. 1979; Müller et al. 1972, 1974, 1975; Nomiyama 1971; Nomiyama and

Nomiyama 1977; Ogata et al. 1971; Skender et al. 1993; Stewart et al. 1970; Vartiainen et al. 1993). A linear correlation was reported between the concentration of trichloroethylene in breathing zone air and the resulting urinary levels of trichloroethanol and TCA recorded within the day (Inoue et al. 1989). However, because urinary TCA has a longer half-life than trichloroethanol, it better reflects long-term exposure, whereas urinary trichloroethanol has been recommended as an indicator of recent exposure (Ulander et al. 1992). Lash et al. (1999a) detected the GSH-derived conjugate of trichloroethylene (DCVG) in the blood of all male and female subjects from 30 minutes after the start of a 4-hour exposure to trichloroethylene vapors at 50 or 100 ppm to up to 8 hours after the end of the exposure period. DCVG levels were approximate 3.5-fold higher in males than females.

There are two biological exposure indices (BEIs) for exposure to trichloroethylene at the ACGIH threshold limit value (TLV-TWA) of 10 ppm (ACGIH 2012). When measured at the end of an 8-hour shift at the end of a 40-hour workweek, the BEI for TCA in urine is 15 mg/g creatinine and the BEI for trichloroethanol in the blood is 0.5 mg/L.

The use of the methods for monitoring metabolites of trichloroethylene in blood and urine is rather limited since the levels of TCA in urine have been found to vary widely, even among individuals with equal exposure (Vesterberg and Astrand 1976). Moreover, exposure to other chlorinated hydrocarbons such as tetrachloroethane, tetrachloroethylene, and 1,1,1-trichloroethane would also be reflected in an increase in urinary excretion of TCA. In addition, there may be sex differences regarding the excretion of trichloroethylene metabolites in urine since one experiment shows that trichloroethylene-exposed men excreted more trichloroethanol than similarly-exposed women (Inoue et al. 1989).

Differences in relevant physiological parameters among individuals can partially explain the differences in the before-workshift and end-of-workshift levels of trichloroethylene and its metabolites. Increased respiration rate during a workday, induced by physical workload, has been shown to affect levels of unchanged trichloroethylene more than its metabolites, while the amount of body fat influences the levels of the solvent and its metabolites in breath, blood, and urine samples before workshift exposure (Sato 1993). Additionally, liver function affects measurements of exhaled solvent at the end of workshift; increased metabolism of trichloroethylene will tend to decrease the amount exhaled after a workshift. Differences in renal output would affect levels of TCA and trichloroethanol in blood before a workshift in the same way, but it probably would not affect urine values between the beginning and the end of the workshift because of the slow excretion rate of TCA.

Results of Brogren et al. (1986) indicate that urinary concentration of the renal tubular enzyme, NAG, may be used as an indicator of renal damage resulting from exposure to chlorinated organic solvents such as trichloroethylene. Other studies specifically examining the influence of factors such as age or alcohol consumption on associations between trichloroethylene exposure and NAG levels have found a weak, nonsignificant correlation (Rasmussen et al. 1993b; Selden et al. 1993).

Serum bile acid levels, which are indicative of liver function, have been shown to increase in a dose-dependent manner in rats exposed via inhalation to trichloroethylene (Wang and Stacey 1990), as well as in occupationally exposed humans (Driscoll et al. 1992). Subsequent investigations revealed that these increases in rats occurred at exposure concentrations that produced no evidence of liver cell damage, thus suggesting that this assay is a sensitive indicator of low-level exposure (Bai and Stacey 1993; Hamdan and Stacey 1993). In contrast, a study of metal degreasers found that the association between the level of γ-glutamyltransferase enzyme (another indicator of liver function) and trichloroethylene exposure became nonsignificant after controlling for the effects of age and alcohol consumption (Rasmussen et al. 1993b).

3.8.2 Biomarkers Used to Characterize Effects Caused by Trichloroethylene

The nervous system is a target of toxicity from acute inhalation exposure to trichloroethylene. However, effects such as dizziness and drowsiness can occur for many reasons and cannot be used as biomarkers for exposure to trichloroethylene. Cranial nerves V and VII are specific targets of trichloroethylene and/or its metabolites, but conclusive studies distinguishing the toxicity of trichloroethylene, its metabolites, and combinations thereof have not been found. A sensitive test, blink reflex latency, can determine damage to the nerves, and it has been used to show prolonged effects from exposure to trichloroethylene in the drinking water at concentrations as high as 200–400 ppb (Feldman et al. 1988). Other neurological functional tests from well-documented neurobehavioral test batteries (e.g., WHO Neurobehavioral Core Test Battery, Neurobehavioral Evaluation System; ATSDR Adult Environmental Neurobehavioral Test Battery) or measurement of sensory-evoked potentials could be useful for screening individuals in the context of documented trichloroethylene exposure (ATSDR 1995; Arezzo et al. 1985; Baker et al. 1985).

The chlorinated hydrocarbons as a class are known to affect the liver and kidney. To determine the potential for human kidney damage resulting from workplace air exposure to trichloroethylene, urinary total protein and β2-microglobulin were tested. These were measured in the urine of workers who had a history of exposure to approximately 15 ppm trichloroethylene (duration of exposure and age were 8.4±7.9 and 36.6±13.6 years, respectively) (Nagaya et al. 1989b). Slight increases in urinary total protein

and β2-microglobulin were noted in the exposed population when compared to controls, except for a significant change in the 35–44-year-old workers. The authors of this study concluded that the adverse effect on the kidney was mild and glomerular rather than tubular. In contrast, Brogren et al. (1986) found increased urinary excretion of N-acetyl-β-D-glucosaminidase, which is released upon necrosis of renal tubular cells in workers exposed to trichloroethylene, trichloroethane, and freon. Both of these markers (β2-microglobulin and N-acetyl-β-D-glucosaminidase) are indicators of kidney damage, but neither marker is specific to trichloroethylene-induced damage; a number of short-chain halogenated hydrocarbons can produce similar effects. Similarly, changes in serum levels of total protein have been used to assess exposure to trichloroethylene, but are not specific to trichloroethylene (Konietzko and Reill 1980; Rasmussen et al. 1993b).

Bolt et al. (2004) reported increased urinary α_1-microglobulin in trichloroethylene-exposed renal cancer patients compared to renal cancer patients and healthy controls without trichloroethylene exposure. Although increased urinary α_1-microglobulin may serve as an indicator of renal toxicity, it is not unique to trichloroethylene exposure.

Brüning et al. (1999) reported increased glutathione-S-transferase alpha (a marker of distal renal tubular damage) in the urine of 39 workers exposed to high levels of trichloroethylene for up to 19 years compared to a group of 46 male office and administrative workers without known exposure to trichloroethylene. However, glutathione-S-transferase levels do not represent a biomarker of effects unique to trichloroethylene, because levels of this enzyme are affected by numerous other xenobiotics. Tabrez and Ahmad (2009) observed increased glutathione-*S*-transferase activity in the liver and kidneys (50 and 218% greater than that of controls) of rats administered trichloroethylene by gavage at 1,000 mg/kg/day for 15 days.

Increased urinary kidney injury molecule-1 levels were reported among trichloroethylene-exposed workers in China (Vermeulen et al. 2012). Kidney injury molecule-1 is a transmembrane protein expressed in dedifferentiated proximal tubular epithelial cells within damaged regions (Huo et al. 2010) and has been shown to outperform traditional biomarkers of renal injury (serum creatinine and BUN) in rat studies (Vaidya et al. 2010). However, as is the case for other potential biomarkers discussed above, increased kidney injury molecule-1 is not specific to trichloroethylene exposure.

3.9 INTERACTIONS WITH OTHER CHEMICALS

Alcohol can affect the metabolism of trichloroethylene. This is noted in both toxicity and pharmacokinetic studies. In a controlled study of male volunteers, consumption of alcohol following 3- or 7.5-hour exposures to trichloroethylene vapors at 200 ppm resulted in approximately 2-fold higher mean trichloroethylene levels in expired air than levels measured without consumption of alcohol (Stewart et al. 1974c). These subjects also showed “degreaser's flush”, a transient vasodilation of superficial skin vessels. In rats, trichloroethylene-induced depressant effects in the central nervous system were exacerbated by oral administration of ethanol (Utesch et al. 1981).

Ethanol administration can potentially increase or decrease trichloroethylene metabolism, depending on two factors: the time interval between ethanol and trichloroethylene administration, and the doses administered. With a short time interval, ethanol and trichloroethylene compete for enzymatic sites, decreasing trichloroethylene metabolism. For example, increased blood levels of trichloroethylene and decreased blood levels of trichloroethanol and TCA were observed in rabbits given ethanol 30 minutes prior to trichloroethylene (White and Carlson 1981). Alternatively, with an extended time interval (e.g., 24–36 hours) after ethanol administration, necessary to enzyme induction, trichloroethylene metabolic rates would be expected to increase. This may explain the decreased blood levels of trichloroethylene that were measured with increased urinary excretion of total trichlorocompounds (trichloroethanol and TCA) when ethanol was given to rats 18 hours prior to inhalation exposure to 500 ppm trichloroethylene (Sato et al. 1981). In a similar study, rats were pre-exposed to a 3-week ethanol, low-carbohydrate, high-fat diet (to induce cytochrome P-450) prior to trichloroethylene inhalation. When compared with rats fed control diets, the pre-exposed rats had significant increases in urinary metabolites at high trichloroethylene concentrations (>500 ppm) (Kaneko et al. 1994).

When trichloroethylene is metabolized to chloral hydrate by the cytochrome P-450 system, the chloral hydrate is either oxidized by chloral hydrate dehydrogenase to TCA or reduced by alcohol dehydrogenase to trichloroethanol (Sato et al. 1981). The oxidation steps require the oxidized form of nicotinamide adenine dinucleotide (NAD^+), while the reduction steps require the reduced form NADH. Ethanol is known to alter the ratio of NAD^+/NADH in hepatocytes and to produce a subsequent shift toward reduction to trichloroethanol. Support for this was found in studies with rats that were exposed to trichloroethylene with and without ethanol. Ethanol coadministration resulted in an increased urinary trichloroethanol/TCA ratio at all dose levels, consistent with the hypothesis of a more reduced state in the hepatocyte caused by generation of excessive reducing agents by ethanol metabolism (Larson and Bull

1989). It should be noted that the lowest doses employed in this study were 200 mg/kg trichloroethylene and 70 mg/kg ethanol.

Other low molecular weight alcohols (e.g., isopropanol), as well as other compounds that inhibit alcohol metabolizing enzymes (e.g., alcohol dehydrogenase) and the hepatic drug metabolizing system, have been shown to alter steady-state blood levels of trichloroethylene. When administered orally to female rats in conjunction with trichloroethylene inhalation exposures, disulfiram, isopropanol, pyrazole, and tetrachloroethylene each increased the steady-state concentration of trichloroethylene in the venous blood (Jakobson et al. 1986). Treatment with disulfiram (an inhibitor of alcohol dehydrogenase) resulted in a significant increase in the amount of trichloroethylene exhaled by women exposed to 186 ppm for 5 hours (Bartonicek and Teisinger 1962). Excretion of trichloroethanol and TCA in the urine decreased by 40–64 and 72–87%, respectively. By enhancing the metabolism of trichloroethylene to its cytotoxic metabolites, compounds that induce the hepatic monoxygenase system can potentiate the hepatotoxicity of trichloroethylene. Pretreatment with phenobarbital and 3-methylcholanthrene, which like ethanol, are inducers of the liver monoxygenase system, increased the extent of liver injury following exposure to trichloroethylene (Carlson 1974). Similar results were found with other inducers of the hepatic monoxygenase system (Allemand et al. 1978; Moslen et al. 1977; Nakajima et al. 1990b). Cheikh Rouhou et al. (2013) assessed the effects of selected pharmaceuticals on the rate of trichloroethylene metabolism in rat hepatocytes *in vitro*. TCA and trichloroethanol levels were increased by naproxen and salicylic acid and decreased by acetaminophen, cimetidine, diclofenac, gliclazide, and valproic acid. Erythromycin and sulphasalazine decreased TCA, (but not trichloroethanol) levels.

Animal studies indicate that high concentrations of trichloroethylene can sensitize the heart to epinephrine-induced arrhythmias, albeit at relatively high trichloroethylene doses. Other chemicals can affect these epinephrine-induced cardiac arrhythmias in animals exposed to trichloroethylene. Phenobarbital treatment, which increases the metabolism of trichloroethylene, has been shown to reduce the trichloroethylene-epinephrine-induced arrhythmias in rabbits (White and Carlson 1979), whereas high concentrations of ethanol, which inhibits trichloroethylene metabolism, have been found to potentiate trichloroethylene-epinephrine-induced arrhythmias in rabbits (White and Carlson 1981). These results indicate that trichloroethylene itself (and not a metabolite) is responsible for the epinephrine-induced arrhythmias. In addition, caffeine has been found to increase the incidence of epinephrine-induced arrhythmias in rabbits exposed to trichloroethylene; the caffeine treatment had no effect on trichloroethylene blood concentration, but caused a reduction in blood trichloroethanol and TCA levels (White and Carlson 1982). The investigators speculated that caffeine may have caused this effect by

stimulating the release of catecholamines from the adrenal medulla and thus elevating circulating levels of epinephrine or by stimulating the release of norepinephrine from adrenergic nerve endings.

Trichloroethylene may occur in drinking water along with other chlorinated hydrocarbons, so effects of these chemicals in combination are of interest to public health. Hepatotoxicity, as measured by plasma enzyme activity, was increased synergistically in rats by oral administration of carbon tetrachloride combined with trichloroethylene (Borzelleca et al. 1990). In addition, synergistic effects were implicated in a 3-day study in which rats were pretreated with trichloroethylene, and then subsequently challenged with carbon tetrachloride, both administered intraperitoneally by gavage or in drinking water (Steup et al. 1991). Trichloroethylene exposure enhanced the subsequent carbon tetrachloride challenge, as measured by increased liver necrosis and plasma ALT levels, although the study authors noted that the exposure levels were far above those normally encountered by humans in their drinking water. In a follow-up study, a single gavage dose of trichloroethylene (0.5 mL/kg) had no toxic effects, but when it was coadministered with carbon tetrachloride, the time-course for synergistic action (measured by a decline of serum ALT and SDH levels and an increase in hepatocyte damage) followed the decline of the GSH level (Steup et al. 1993). This finding may either implicate GSH in the trichloroethylene potentiation of carbon tetrachloride toxicity or simply be a result of general hepatic injury. Concurrent administration of trichloroethylene and tetrachloroethylene to mice did not result in additive or synergistic effects in induction of hepatic peroxisomal proliferation, as measured by cyanide-insensitive palmitoyl CoA oxidation activity (Goldsworthy and Popp 1987). In a PBPK modeling exercise designed to analyze data describing the metabolism of vinyl chloride and trichloroethylene mixtures in rats, a single saturable pathway representing CYP2E1 was modeled; results from the modeling exercise and *in vitro* assays indicated that competitive inhibition of cytochrome P-450 metabolism was elicited by mixtures of vinyl chloride and trichloroethylene (Barton et al. 1995).

A study examining the effects of trichloroethylene and styrene inhalation on the rat auditory system found that the combined effect of these compounds was additive, suggesting that their mechanisms of action are similar (Rebert et al. 1993). A 5-day exposure to 1,500 ppm trichloroethylene had no effect on brainstem auditory-evoked response unless combined with a simultaneous exposure to 500 ppm styrene, in which case substantial hearing loss was noted. Co-exposure to trichloroethylene and other chemicals that are metabolized by common cytochrome P450 isozymes to reactive metabolites would be expected to result in decreased trichloroethylene toxicity due to competitive metabolic inhibition and resulting decreased metabolic activation.

Coexposure to mercury was reported to increase trichloroethylene-induced autoimmune hepatitis in autoimmune-prone MRL+/+ mice (Gilbert et al. 2011). Co-exposure to trichloroethylene and mercury also generated a liver-specific antibody response in the mice that was not observed in mice exposed to mercury or trichloroethylene alone.

Muijser et al. (2000) reported that mice exposed to trichloroethylene vapors (3,000 ppm) and noise (95 dB) experienced significantly greater hearing loss at the 4 kHz frequency than mice exposed to either trichloroethylene or noise alone; the results were considered indicative of an interaction between exposures to trichloroethylene and noise in combination.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

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

The elderly with declining organ function and the youngest of the population with immature and developing organs (i.e., premature and newborn infants) will be more vulnerable to toxic substances in general than healthy adults. As discussed in Section 3.7 (Children's Susceptibility), infants and young children may be more susceptible than adults to trichloroethylene toxicity based on age-related differences in the pharmacokinetics of trichloroethylene. For example, trichloroethylene may be absorbed in greater concentrations in children exposed by inhalation due to increased ventilation rates (e.g., inspired volume per minute per kg body weight per unit alveolar surface area) and increased cardiac output per kg body weight compared to adults (EPA 2008; NRC 2009; Snodgrass 1992). Intake from trichloroethylene-contaminated drinking water is expected to be greater in children than adults because children tend to drink more water on a per kg body weight basis than adults. Nursing infants can be exposed to trichloroethylene via the breast milk (Pellizzari et al. 1982). Household dust and dirt are potential sources of greater potential dermal contact and ingestion exposure in small children, although no information was located regarding trichloroethylene levels in household dust or dirt. At comparable absorption levels, lipophilic substances such as trichloroethylene may become more concentrated in the

fat of infants and small children due to their lower amounts of fat per kilogram body weight compared to adolescents and adults (NRC 1993). In cases where metabolic products are more toxic than the parent compound, an individual with higher metabolic rates (as may occur in some children and adolescents) would be expected to have greater toxicity; conversely, lower metabolic rates would be expected to result in a lesser degree of toxicity.

Some people who have worked with trichloroethylene for long periods of time may develop an allergy to it or become particularly sensitive to its effects on the skin (e.g., Bauer and Rabens 1974; Chittasobhaktra et al. 1997; Czirjak et al. 1993; El Ghawabi et al. 1973; Goh and Ng 1988; Hayashi et al. 2000; Huang et al. 2006; Kamijima et al. 2007; Pantucharoensri et al. 2004; Xu et al. 2009). People who consume alcohol or who are treated with disulfiram may be at greater risk of trichloroethylene poisoning because ethanol and disulfiram can both inhibit the metabolism of trichloroethylene and can cause it to accumulate in the bloodstream, potentiating its effects on the nervous system. Compromised hepatic and renal function may place one at higher risk upon exposure to trichloroethylene or its metabolites since the liver serves as the primary site of trichloroethylene metabolism and the kidney serves as the major excretory organ for trichloroethylene metabolites. When trichloroethylene was used as an anesthetic or inhaled in high concentrations intentionally or occupationally, it caused cardiac arrhythmias in some people. Thus, some individuals with a history of cardiac rhythm disturbances may be more susceptible to high-level trichloroethylene exposure. Results of a study in which trichloroethylene-exposed workers with generalized skin disorders accompanied by hepatic dysfunction and healthy trichloroethylene-exposed workers were assessed for possible risk factors for rash and hepatitis indicated that those with human herpesvirus 6 were more likely to suffer trichloroethylene-induced skin disorders and hepatic dysfunction (Huang et al. 2006). Giovanetti et al. (1998) found increased numbers of vacuolated Clara cells in the lungs of mice administered a copper-deficient diet and exposed to trichloroethylene vapors.

The metabolism of trichloroethylene, as measured by the levels of excreted urinary metabolites, may differ between men and women (Inoue et al. 1989; Kimmerle and Eben 1973b; Nomiyama and Nomiyama 1971). For example, it has been reported that women excrete more urinary TCA (a metabolite of trichloroethylene and other chlorinated substances such as tetrachloroethylene) than do men (Kimmerle and Eben 1973b; Nomiyama and Nomiyama 1971). Lash et al. (1999a) reported that trichloroethylene-exposed male subjects produced approximately 3.5-fold higher levels of DCVG in the blood than similarly-exposed female subjects, indicating that males may be more susceptible to trichloroethylene-induced renal toxicity. Testosterone has been implicated as a factor in the lower dermal absorption of trichloroethylene in male rats compared with females (McCormick and Abdel-Rahman 1991).

There is some indication of gene-related susceptibility to trichloroethylene toxicity. Selected genotypes/phenotypes may be more sensitive to trichloroethylene based on differences in metabolic rates (Brüning and Bolt 2000; Dai et al. 2009; Moore et al. 2010; NRC 2009). Li et al. (2007) reported an association between the presence of a particular allele for human leucocyte antigen (HLA-B*1301) and hypersensitivity dermatitis among trichloroethylene-exposed workers.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to trichloroethylene. 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 trichloroethylene. When specific exposures have occurred, poison control centers, board certified medical toxicologists, board-certified occupational medicine physicians, and/or other medical specialists with expertise and experience treating patients overexposed to trichloroethylene can be consulted for medical advice. The following texts provide specific information about treatment following exposures to trichloroethylene:

Gummin DD. 2015. Hydrocarbons. In: Hoffman RS, Lewin NA, Goldfrank LR, et al., eds. Goldfrank's toxicologic emergencies. Tenth ed. New York, NY: McGraw-Hill Education, 309-310, 1334.

Shusterman D. 2018. Trichloroethane, trichloroethylene and tetrachloroethylene. In: Olson R, Olson IB, Anderson NL, et al., eds. Poisoning and drug overdose: Section II: Specific poisons and drugs: Diagnosis and treatment. Seventh ed. New York, NY: McGraw-Hill.

Palmer RB, Phillips SD. 2007. Chlorinated hydrocarbons. In: Shannon MW, Borron SW, Burns MJ. Haddad and Winchester's clinical management of poisoning and drug overdose. 4th ed. Philadelphia, PA: Saunders Elsevier, 1347-1361.

The front of the profile contains the QUICK REFERENCE FOR HEALTH CARE PROVIDERS that provides additional relevant information.

3.11.1 Reducing Peak Absorption Following Exposure

Human exposure to trichloroethylene may occur by inhalation, ingestion, or dermal contact. Mitigation methods for reducing exposure to trichloroethylene have included the general recommendations of separating contaminated food, water, air, and clothing from the exposed individual (HSDB 2013).

The following recommendations for treating trichloroethylene poisoning are taken from Grummin (2014) and Shusterman et al. (2018). There is no specific antidote. Following suspected overexposure to trichloroethylene, the person should be promptly placed under the care of a knowledgeable physician. In the case of vapor exposure, the person should be removed from the vapor-contaminated environment and given the standard emergency and supportive treatment. Anesthetic overexposure may require respiratory assistance and the treatment of cardiac arrhythmias. Do not induce emesis or administer activated charcoal. In the case of eye exposure, irrigation with copious amounts of water or saline has been recommended. For dermal exposure, the removal of contaminated clothing and a thorough washing of any exposed areas with mild soap and water have been recommended.

3.11.2 Reducing Body Burden

No methods to reduce body burden of trichloroethylene have been identified (Shusterman et al. (2018). Trichloroethylene is exhaled following inhalation and oral exposures, whereas metabolites are mainly excreted in the urine. See Sections 3.4.3 (Toxicokinetics, Metabolism) and 3.4.3 (Toxicokinetics, Elimination and Excretion) for a more detailed discussion of metabolism and excretion of trichloroethylene and metabolites.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

The mechanism of action of trichloroethylene in the body is not well understood, and there are no proven methods of interfering with the mechanism of action for toxic effects. Based on the limited understanding of the mechanisms of action, methods of interference can be suggested. These methods require additional research before they can be put into use.

Reports of cardiac arrhythmias following exposure to trichloroethylene are not uncommon (Bell 1951; Kleinfeld and Tabershaw 1954; Morreale 1976; Smith 1966). Anti-adrenergic agents, such as propranolol and esmolol, block β-adrenergic receptors, thus preventing catecholamines such as epinephrine from binding; these agents may be useful in preventing cardiac arrhythmias that can occur with exposure to trichloroethylene. The consequences of using a β-adrenergic blocker for treatment of high exposure to trichloroethylene must be taken into consideration. Catecholamines (especially beta agonists) act in concert with trichloroethylene, increasing the risk of cardiac arrhythmias. Hence, catecholamines should be avoided if possible. Ethanol should also be avoided because concurrent exposure to trichloroethylene and ethanol can cause vasodilation and malaise and may potentiate central nervous system depression at high dosage levels of either compound. Because physical activity appears to increase the chance of

cardiac effects, reducing physical exertion after exposure to trichloroethylene may be useful. Reduction of stress may be helpful by reducing catecholamine release. Oxygen therapy might be useful, as hypoxia potentiates trichloroethylene-induced arrhythmias.

Administration of antioxidants such as curcumin diminished trichloroethylene-induced oxidative stress in mouse liver cells (Watanabe and Fukui 2000); however, this response was only demonstrated *in vitro*. Trichloroethylene has been shown to decrease methylation of the *c-jun* and *c-myc* protooncogenes and increase levels of their messenger ribonucleic acid (mRNA) in the livers of mice (Tao et al. 2000). Co-treatment with methionine prevented both decreased methylation and increased levels of the mRNA and proteins of the *c-jun* and *c-myc* protooncogenes. The study authors hypothesized that trichloroethylene may act as a carcinogen by depleting the availability of S-adenosylmethionine and that methionine could prevent DNA hypomethylation by maintaining sufficient S-adenosylmethionine. However, methionine treatment has not been suggested as a method for protecting against trichloroethylene carcinogenicity.

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 trichloroethylene 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 adverse health effects (and techniques for developing methods to determine such health effects) of trichloroethylene.

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 risk 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 Trichloroethylene

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to trichloroethylene are summarized in Figure 3-24. The purpose of this figure is to illustrate the existing information concerning the health effects of trichloroethylene. Each dot in the figure indicates that one or

Figure 3-24. Existing Information on Health Effects of Trichloroethylene

	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
	Systemic									
Inhalation	●	●	●	●		●	●	●	●	●
Oral	●	●	●	●	●	●		●		●
Dermal		●	●	●						

Human

	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
	Systemic									
Inhalation	●	●	●	●	●	●	●	●	●	●
Oral	●	●	●	●	●	●	●	●	●	●
Dermal	●	●								●

Animal

● Existing Studies

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* (ATSDR 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.

Studies of workers and volunteers have provided most of the data on health effects of inhaled trichloroethylene in humans. Most of the information on reported effects in humans following oral exposure is from data of questionable validity on populations exposed to well water contaminated with trichloroethylene and other compounds. Information regarding lethality in humans resulting from inhalation or oral exposure is limited to case reports of acute exposures that are poorly quantified at best.

Data are available for central nervous system effects in humans resulting from acute and chronic inhalation exposure. A few reports of acute oral and inhalation exposures have indicated that adverse hepatic and renal effects occur in humans. As discussed in detail in Sections 3.2.1.7 and 3.2.2.7, numerous reports are available regarding possible associations between exposure to trichloroethylene and risk for cancer. EPA (2011e) developed quantitative estimates of cancer risk based on results of a case-control study that reported a statistically significant association between self-reported occupational exposure to trichloroethylene and occurrence of renal cancer (Charbotel et al. 2006) and adjusted for potential risk for non-Hodgkin's lymphoma and liver cancer. Quantitative estimates included an inhalation unit risk if 0.02 per ppm and an oral slope factor of 0.05 per mg/kg/day that was derived using PBPK model-based route-to-route extrapolation of the inhalation unit risk.

Studies have been performed in animals that cover all of the health effects areas listed in Figure 3-24 for inhalation and oral exposure. Few dermal data exist, other than case reports of effects in humans following acute exposures, animal lethality data, and one animal carcinogenicity study. Studies with animals identify the general range of lethality and principal toxic effects of inhalation and oral exposure to trichloroethylene. Although trichloroethylene toxicity has been extensively studied, quantitative dose-response data are insufficient to fully characterize effects for some of the critical targets. One of the limitations to interpreting results from some of the oral studies is that they employ bolus or gavage administration of trichloroethylene in oil (often corn oil), which do not adequately represent kinetics relevant to an exposure to trichloroethylene in drinking water.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. Deaths have resulted from the early use of trichloroethylene as an anesthetic (DeFalque 1961), from accidental exposure to unusually high levels in workplace environments (Bell 1951; Coopman et al. 2003; Ford et al. 1995; James 1963; Kleinfeld and Tabershaw 1954; McCarthy and Jones 1983; Pantucharoensri et al. 2004; Smith 1966; Thorburn et al. 2004), and from the presumed intentional inhalation of concentrated fumes from trichloroethylene-containing substances (Clearfield 1970; Jones and Singer 2008; Takaki et al. 2008; Troutman 1988). Two acute lethality studies are available for animals (Kylin et al. 1962; Siegel et al. 1971). Cardiac effects including tachycardia, ECG abnormalities, and arrhythmias have been reported in humans following acute inhalation exposure (Clearfield 1970; DeFalque 1961; Dhuner et al. 1957; Gutch et al. 1965; Hewer 1943; Pembleton 1974). A number of human deaths following acute inhalation exposure to trichloroethylene exposure have been attributed to cardiac effects (Bell 1951; Ford et al. 1995; Kleinfeld and Tabershaw 1954; Troutman 1988). Deaths of humans often occurred following physical exertion. Acute inhalation studies in animals reveal that trichloroethylene sensitizes the heart to catecholamines (Reinhardt et al. 1973; White and Carlson 1979, 1981, 1982). In cases of acute accidental or intentional overexposure to trichloroethylene, neurological effects include euphoria, giddiness, lethargy, confusion, dizziness, headache, nausea, difficulty swallowing, facial effects that indicate possible trigeminal nerve damage (including sensation deficits, jaw weakness, increased blink reflex latency), which may be irreversible, memory deficits, and unconsciousness (Adamek and Krupiński 2007; Buxton and Hayward 1967; Carrieri et al. 2007; Clearfield 1970; Feldman 1970; Feldman et al. 1985; James 1963; Lawrence and Partyka 1981; Lachnit and Pietschmann 1960; Leandri et al. 1995; Longley and Jones 1963; Milby 1968; Miller et al. 2002; Pembleton 1974; Thierstein et al. 1960; Troutman 1988).

Sufficient human and animal information is available to identify the nervous system as a sensitive target for the acute effects of trichloroethylene encountered via the inhalation route. The chemical was once used as a surgical anesthetic, so its central nervous system depressant effects in humans are well known. Experimental exposures have revealed decrements in complex reaction time, immediate memory, and perception in humans inhaling 110 ppm for 8 hours (Salvini et al. 1971). However, other human studies have shown that the effect threshold may be somewhat higher (Ettema et al. 1975; Stewart et al. 1970; Vernon and Ferguson 1969) or lower (Nomiyama and Nomiyama 1977). The Nomiyama and Nomiyama (1977) study is limited by the use of only three test subjects for each exposure concentration, lack of statistical analysis, sporadic occurrence of the effects, and a lack of a clear dose-response relationship. The cranial nerves (V and VII) may be especially sensitive to trichloroethylene effects. However, it is not

clear if this neuropathy results from trichloroethylene exposure directly because there is evidence that damage to these nerves may result from exposure to the trichloroethylene decomposition product dichloroacetylene.

Additional adverse effects noted in humans following acute inhalation exposure to trichloroethylene include nausea and vomiting (Clearfield 1970; David et al. 1989; DeFalque 1961; Gutch et al. 1965; Lachnit and Pietschmann 1960), mild evidence of liver damage (Clearfield 1970), renal failure (David et al. 1989; Gutch et al. 1965), and muscle necrosis (Thorburn et al. 2004); the single case of muscle necrosis included a dermal exposure component. Additional adverse effects noted in animals following acute inhalation exposure to trichloroethylene include liver damage (Carlson 1974; Fujita et al. 1984; Okino et al. 1991), kidney damage (Chakrabarti and Tuchweber 1988; Crofton and Zhao 1993), and respiratory effects (Odum et al. 1992; Villaschi et al. 1991).

Acute oral LD_{50} values are available from animal studies (Smyth et al. 1969; Tucker et al. 1982). Following acute oral exposure to trichloroethylene, effects noted in humans include neurological effects (Dhuner et al. 1957; Morreale 1976; Perbellini et al. 1991; Stephens 1945; Todd 1954), gastrointestinal effects (De Baere et al. 1997; Liotier et al. 2008; Moritz et al. 2000; Vattemi et al. 2005), cardiac effects (Brüning et al. 1998; Dhuner et al. 1957; Moritz et al. 2000; Morreale 1976; Perbellini et al. 1991; Vattemi et al. 2005), hepatic effects (Kleinfeld and Tabershaw 1954), pulmonary effects (De Baere et al. 1997), and musculoskeletal effects (Vattemi et al. 2005). Effects noted in animals following acute oral exposure to trichloroethylene include hepatic effects (Atkinson et al. 1993; Berman et al. 1995; Dees and Travis 1993; Elcombe 1985; Elcombe et al. 1985; Goldsworthy and Popp 1987; Stott et al. 1982), renal effects (Berman et al. 1995), neurological effects (Moser et al. 1995; Narotsky and Kavlock 1995; Narotsky et al. 1995; Nunes et al. 2001), and immunological effects (Sanders et al. 1982).

Further studies on the developmental neurological effects of trichloroethylene in both animals and humans could contribute to more fully characterizing these effects.

Pain and erythema have been reported by study subjects who placed their hands (Sato and Nakajima 1978) or thumbs in trichloroethylene (Stewart and Dodd 1964). Application of trichloroethylene to the skin of guinea pigs resulted in erythema and edema.

Additional information regarding doses/concentrations that result in cardiac effects and conditions that may make persons more sensitive to these effects would be beneficial, although such information is not likely due to present-day occupational exposure limits.

When accidental human exposures occur, investigations to determine trichloroethylene exposure levels might add valuable information regarding exposure-response relationships. Similarly, studies on the acute effects of dermal exposure to trichloroethylene in animals may be useful in determining the risk for these exposures in humans at hazardous waste sites. However, there appear to be sufficient data regarding neurological effects after acute inhalation exposure.

Intermediate-Duration Exposure. Neurological effects are the most consistent effects reported in humans exposed to trichloroethylene for intermediate exposure durations (Mitchell and Parsons-Smith 1969; Steinberg 1981). Caprioli et al. (2001) reported loss of strength and polyneuropathy in a woman who had been exposed to trichloroethylene during a 3-month period of degreasing and antiquing processes (7–8 hours/day) in a poorly-ventilated garage. In a group of patients diagnosed with hypersensitivity dermatitis where the average trichloroethylene exposure time was 38.2 days (range 5–90 days), estimated trichloroethylene air concentrations were in the range of 18–683 mg/m^3 (3.24–122.9 ppm) (Xu et al. 2009). Stevens-Johnson syndrome, a severe dermatologic reaction, was seen in five people occupationally exposed to trichloroethylene for 2–5 weeks at levels ranging from 19 to 164 ppm (Phoon et al. 1984). Body weight loss has been reported in humans occupationally exposed to trichloroethylene for intermediate or chronic durations at concentrations resulting in neurological effects (Mitchell and Parsons-Smith 1969; Schattner and Malnick 1990).

Effects of trichloroethylene exposure in animals following intermediate-duration inhalation exposures include neurological effects (Adams et al. 1951; Albee et al. 1993, 2006; Arito et al. 1994a; Baker 1958; Battig and Grandjean 1963; Blain et al. 1992; Boyes et al. 2000, 2003, 2005; Crofton and Zhao 1997; Fechter et al. 1998; Goldberg et al. 1964a; Haglid et al. 1981; Jaspers et al. 1993; Kulig 1987; Muijser et al. 2000; Rebert et al. 1991; Silverman and Williams 1975; Waseem et al. 2001), respiratory effects (Kumar et al. 2002b), hepatic effects (Adams et al. 1951; Kjellstrand et al. 1983a; Kumar et al. 2001a), kidney effects (Mensing et al. 2002), endocrine effects (Kumar et al. 2000a), developmental effects (Blossom et al. 2008; Dawson et al. 1993; Dorfmueller et al. 1979; Johnson et al. 1998, 2003; Peden-Adams et al. 2006), and body weight effects (Adams et al. 1951; Kjellstrand et al. 1983a; Kumar et al. 2001b).

Available information regarding health effects in humans following intermediate-duration oral exposure to trichloroethylene is limited to studies examining reproductive outcome in people exposed to trichloroethylene in drinking water (ATSDR 1997; MDPH 1996). Effects in animals following intermediate-duration oral exposure include neurological effects (Barret et al. 1991, 1992; Gash et al. 2008; Isaacson et al. 1990), liver effects (Buben and O'Flaherty 1985; Merrick et al. 1989; NTP 1985, 1986; Stott et al. 1982), respiratory effects (NTP 1990), kidney effects (NTP 1985, 1990; Tucker et al. 1982), gastrointestinal effects (Tucker et al. 1982), hematological effects (Tucker et al. 1982), body weight effects (Blossom and Doss 2007; Cai et al. 2008; NTP 1986, 1990; Zenick et al. 1984), and immunological effects (Blossom and Doss 2007; Blossom et al. 2008; Cai et al. 2008; Gilbert et al. 1999; Griffin et al. 2000a, 2000b; Keil et al. 2009; Kobayashi et al. 2010, 2012; Peden-Adams et al. 2006; Sanders et al. 1982; Seo et al. 2008b, 2012; Wang et al. 2007a, 2007b). Intermediate-duration dermal studies of trichloroethylene in humans or animals were not available.

Additional animal studies of trichloroethylene following intermediate-duration oral exposure could further define dose-response relationships. Animal studies of intermediate-duration dermal exposure might be useful in determining whether targets following dermal exposure differ from those identified in inhalation and oral studies.

Chronic-Duration Exposure and Cancer. Studies of humans exposed to trichloroethylene in the air for chronic periods in the workplace provide evidence of trichloroethylene-induced neurological effects (Bardodej and Vyskocil 1956; Barret et al. 1987; Bauer and Rabens 1974; El Ghawabi et al. 1973; Kohlmuller and Kochen 1994; Rasmussen et al. 1993c; Ruijten et al. 1991), liver effects (Bauer and Rabens 1974; Schuttmann 1970), and kidney effects (Brogren et al. 1986). Chronic-duration studies of animals exposed to trichloroethylene via the inhalation route were not located.

Information on chronic human exposure to trichloroethylene via oral and/or dermal routes derives largely from studies of people who consumed trichloroethylene and other solvents from their drinking water for several years and experienced dermal exposure when washing with the contaminated water (ATSDR 1999; Bove et al. 1995; Burg and Gist 1999; Burg et al. 1995; Byers et al. 1988; Cohn et al. 1994; Davis et al. 2005; Fagliano et al. 1990; Feldman et al. 1988; Freni and Bloomer 1988; Goldberg et al. 1990; Kilburn and Warshaw 1992; Lagakos et al. 1986a; Vartiainen et al. 1993; Waller et al. 1994). The effects associated with trichloroethylene in these studies included cardiovascular effects (Byers et al. 1988), dermal effects (Byers et al. 1988; Waller et al. 1994), immunological effects (Byers et al. 1988; Kilburn and Warshaw 1992; Waller et al. 1994), neurological effects (Feldman et al. 1988), increased incidences

of birth defects (Bove et al. 1995; Goldberg et al. 1990; Lagakos et al. 1986a), and cancer (Cohn et al. 1994; Fagliano et al. 1990; Lagakos et al. 1986a). An exposure subregistry was established by ATSDR to monitor people living in areas where they were exposed to trichloroethylene from domestic water sources (ATSDR 1994, 1999; Burg and Gist 1999; Burg et al. 1995; Davis et al. 2005). Data in the Trichloroethylene Subregistry indicate excess prevalence of stroke, anemia (and other blood disorders), liver disease, and skin disorders. There was some evidence of increased prevalence of kidney disease and diabetes as well. The greatest limitations to these studies are the difficulty in estimating dose, and exposure to multiple chemicals.

Chronic oral exposure studies in animals have mainly focused on carcinogenicity and relatively insensitive noncancer end points and are not helpful in defining relatively sensitive noncancer end points in humans following long-term exposure. In one recent study in which mice were exposed to trichloroethylene via their mothers during gestation and lactation and via the drinking water for up to 12 months thereafter, depressed mean terminal body weight was noted at an estimated trichloroethylene oral dose level of 3.3 mg/kg/day and decreased thymic cellularity was noted at estimated doses ≥0.33 mg/kg/day (Peden-Adams et al. 2008). Additional chronic-duration oral studies of trichloroethylene in animals could serve to further define studies that provide information on sensitive end points of trichloroethylene toxicity.

Some workers who have had dermal contact with trichloroethylene have had adverse responses, but potential effects of low levels of trichloroethylene exposure on the skin at hazardous waste sites are not known. Chronic-duration dermal studies in animals were not identified. A chronic-duration dermal study in animals may also be useful to identify critical targets of trichloroethylene toxicity.

The most convincing evidence for an association between exposure to trichloroethylene and cancer in humans is for kidney cancer. Upon critical review of the available epidemiological data regarding the possible carcinogenicity of trichloroethylene, the NRC (2006) and the EPA (2011e) determined that there is convincing evidence for a causal association between trichloroethylene exposure and kidney cancer. The EPA (2011e) performed a meta-analysis using up to 15 cohort and case-control studies considered to be of adequate quality and with a high probability for trichloroethylene exposure to individual subjects and reported a significant association between overall trichloroethylene exposure and increased risk for kidney cancer. EPA (2011e) performed a meta-analysis using up to 16 cohort and case-control studies considered to be of adequate quality and with a high probability for trichloroethylene exposure to individual subjects and reported a slight, but significant, association between overall trichloroethylene

exposure and increased risk for non-Hodgkin's lymphoma. EPA (2011e) performed a meta-analysis using up to nine cohort studies considered to be of adequate quality and with a high probability for trichloroethylene exposure to individual subjects and reported a slight, but significant, association between overall trichloroethylene exposure and increased risk for liver and biliary tract cancer. Some epidemiological studies provide suggestive evidence for an association between trichloroethylene in the drinking water and the occurrence of certain cancers (Byers et al. 1988; Cohn et al. 1994; Fagliano et al. 1990; Kotelchuck and Parker 1979; Lagakos et al. 1986a; MDPH 1997; Parker and Rosen 1981). However, these studies are limited by lack of information regarding individual intake of trichloroethylene and the presence of other drinking water contaminants.

Animal studies have shown chronic-duration inhalation exposure (Fukuda et al. 1983; Henschler et al. 1980; Maltoni et al. 1986) and oral exposure (Anna et al. 1994; Henschler et al. 1984; NCI 1976; NTP 1990) to trichloroethylene can result in tumors. Some of these studies (NCI 1976) are limited in that they use carcinogenic epoxide stabilizers with the trichloroethylene, which may contribute to the carcinogenicity. The studies also show different responses depending on the sex, species, and strains of animals used. Other studies are flawed because of excess mortality. The studies to date indicate that trichloroethylene is carcinogenic in mice, based on the findings of liver cancer in some studies (Fukuda et al. 1983; Henschler et al. 1980; Maltoni et al. 1986; NTP 1990); the evidence for the carcinogenicity of trichloroethylene in rats is equivocal (Maltoni et al. 1986; NTP 1988, 1990), with kidney tumors developing in male rats, but not female rats.

The nephrocarcinogenicity of trichloroethylene has been adequately assessed. Additional human and animal studies should focus on the carcinogenicity of trichloroethylene at other organ and tissue sites. Additional epidemiological studies would be of benefit in assessing health risks for people living near hazardous waste sites. Additional chronic-duration inhalation studies of trichloroethylene in animals could help to define the thresholds of toxicity following chronic inhalation exposure.

Genotoxicity. The genotoxicity studies of trichloroethylene have produced mixed results. Some *in vivo* human and animal data suggest that trichloroethylene may cause genotoxic effects such as gene mutation (Bronzetti et al. 1978; Fahrig 1977), sister chromatid exchange (Gu et al. 1981b; Kligerman et al. 1994), chromosomal aberrations (Rasmussen et al. 1988), single-strand breaks (Nelson and Bull 1988; McLaren et al. 1994; Robbiano et al. 2004; Toraason et al. 1999; Walles 1986), micronuclei (Robbiano et al. 1998, 2004; Sujatha and Hegde 1998), C-mitotic changes (Sujatha and Hegde 1998), DNA damage (Toraason et al. 1999), and DNA and protein adduct formation (Halmes et al. 1997; Kautiainen et al.

1997; Mazzullo et al. 1992). Other *in vivo* studies reported negative results for gene mutations (Rossi et al. 1983), chromosomal aberrations (Beliles et al. 1980; Kligerman et al. 1994; Sujatha and Hegde 1998), micronuclei (Allen et al. 1994; Kligerman et al. 1994), sister chromatid exchange (Nagaya et al. 1989a), single-strand breaks (Parchman and Magee 1982), and DNA damage (Clay 2008; Mirsalis et al. 1989).

Some *in vitro* studies show positive results for such effects as gene mutations, recombination, mitotic aneuploidy, single-strand breaks, micronuclei, DNA damage, cell transformation, and protein adduct formation (Baden et al. 1979; Bartsch et al. 1979; Beliles et al. 1980; Bronzetti et al. 1978; Callen et al. 1980; Crebelli et al. 1985; Griffin et al. 1998; Koch et al. 1988; McGregor et al. 1989; Price et al. 1978; Robbiano et al. 2004; Simmon et al. 1977; Tu et al. 1985). However, many additional studies testing these or other genotoxic effects have been negative (Amacher and Zelljadt 1983; Beliles et al. 1980; Callen et al. 1980; Emmert et al. 2006; Greim et al. 1975; Henschler et al. 1977; Koch et al. 1988; McGregor et al. 1989; Mortelmans et al. 1986; Nagaya et al. 1989a; Rossi et al. 1983; Shimada et al. 1985; Slacik-Erben et al. 1980; Waskell 1978). Currently, the sister chromatid exchange data on the effects of trichloroethylene in humans are confounded by the effects of smoking. More information is needed regarding the effects of trichloroethylene on frequency of sister chromatid exchange in humans who do not smoke. Further investigation is needed regarding chromosomal aberrations and sister chromatid exchange following *in vivo* trichloroethylene exposure in both humans and animals following inhalation (in the workplace) and oral (through contaminated drinking water) routes of exposure.

Reproductive Toxicity. Possible associations between exposure to organic solvents (including trichloroethylene) and measures of fertility and fecundity have been assessed to some extent in occupationally-exposed men and women. Increased miscarriages were reported in one study of nurse-anesthetists exposed to trichloroethylene and other solvents (Corbett et al. 1974). A retrospective case-control study reported an approximate 3-fold increase in spontaneous abortion in women exposed to trichloroethylene and other solvents (Windham et al. 1991). Other epidemiologic studies have evaluated possible associations between occupational exposure of women to organic solvents (including trichloroethylene) and measures of fertility including time-to-pregnancy, spontaneous abortion, and menstrual cycle disturbance (Bardodej and Vyskocil 1956; Corbett et al. 1974; Lindbohm et al. 1990; Sallmén et al. 1995; Taskinen et al. 1994; Windham et al. 1991; Zielinski 1973); none of these studies provided convincing evidence of significant associations between exposure to trichloroethylene and impaired fertility or menstrual cycle disturbance. Some studies have reported reproductive effects in men occupationally exposed to trichloroethylene such as decreased potency or unspecified sexual disturbances (Bardodej and Vyskocil 1956; El Ghawabi et al. 1973) and changes in sperm morphology (Chia et al.

1996, 1997; Goh et al. 1998). Significant effects on sperm parameters were not observed in another study of men occupationally exposed to trichloroethylene (Rasmussen et al. 1988). Sallmén et al. (1998) found no effect on male fertility in a study that examined paternal occupational exposure to trichloroethylene and time-to-pregnancy among their wives. Adverse reproductive effects were not noted in humans who ingested water contaminated with trichloroethylene and other solvents (Byers et al. 1988; Freni and Bloomer 1988; Lagakos et al. 1986a). The human studies are typically limited due to concomitant exposure to other potential reproductive toxicants and lack of quantitative exposure-response data.

Studies in animals demonstrate the toxicity of trichloroethylene to the male reproductive system. Repeated inhalation exposures of male rats or mice to trichloroethylene vapors resulted in effects such as Testicular atrophy, degeneration of epididymal epithelium, changes in sperm morphology, decreases in sperm count and motility, and decreased numbers of sperm capable of attaching to eggs (Beliles et al. 1980; Forkert et al. 2002; Kan et al. 2007; Kumar et al. 2000a, 2000b, 2001b; Land et al. 1981; Xu et al. 2004), Beliles et al. 1980). In a continuous breeding protocol, NTP (1985) reported a 45% decrease in sperm motility in male F0 and F1 mice receiving trichloroethylene from drinking water for up to 18 weeks at a concentration resulting in an estimated dose of 737 mg/kg/day. Reproductive performance was not tested in most of the animal studies. However, Zenick et al. (1984) reported impairment in copulatory behavior, mount/ejaculation latency, and intromissions in male rats administered trichloroethylene by gavage at 1,000 mg/kg/day, 5 days/week for 6 weeks.

There is a need to further assess relationships between exposure to trichloroethylene and reproductive outcomes among humans exposed to trichloroethylene in the workplace and from contaminated drinking water. Additional animal studies should be designed to assess reproductive performance.

Developmental Toxicity. Epidemiological data are typically limited by concomitant exposure to other potentially hazardous substances, and case-control studies are limited by small numbers of cases. Thus, definitive positive associations between exposure to trichloroethylene and the occurrence of developmental effects are not possible from the available data.

There is some evidence of trichloroethylene-related increased rates of birth defects among nurse-anesthetists who were exposed to trichloroethylene and other anesthetic gases during pregnancy (Corbett et al. 1974) and increased risk of spontaneous abortion among women occupationally or nonoccupationally exposed to trichloroethylene and other solvents (Windham et al. 1991). Increased risk of congenital heart defects was reported among offspring of mothers living in the vicinity of

trichloroethylene-emitting sites (ATSDR 2006, 2008; Bove et al. 1995; Forand et al. 2012; Yauck et al. 2004). Increased risk of other birth defects or low birth weight have been reported among populations living in areas with trichloroethylene-contaminated drinking water (ATSDR 1997, 1998; Bove et al. 1995; Goldberg et al. 1990; Lagakos et al. 1986a; MDPH 1996) or where elevated airborne levels of trichloroethylene have been measured (Forand et al. 2012). White et al. (1997) provided evidence of cognitive impairment in children living in areas with reported high levels of trichloroethylene in the drinking water. Oral studies have suggested that exposure to trichloroethylene, along with other volatile hydrocarbons, may increase the risk of childhood leukemia (Lagakos et al. 1986b). An increase in hearing impairment in children ≤9 years old was reported among participants in the ATSDR exposure subregistry for trichloroethylene at baseline assessment, but not at several follow-up timepoints (ATSDR 1994, 1999, 2002; Burg and Gist 1999; Burg et al. 1995; Davis et al. 2005). Firm conclusions on the levels of trichloroethylene that might be associated with adverse birth outcomes or developmental effects in growing children are not possible from the existing database. There are no known studies in humans of developmental effects from dermal exposure to trichloroethylene.

Limited information is available regarding the developmental toxicity of trichloroethylene in animals exposed by the inhalation route. Decreased fetal weight and incomplete ossification were reported in fetuses of rats exposed to trichloroethylene vapors during gestation at exposure levels that were not overtly toxic to the dams (Dorfmueller et al. 1979). There were no indications of trichloroethylene-induced developmental effects in other rat or mouse studies that employed the inhalation exposure route (Beliles et al. 1980; Carney et al. 2006; Hardin et al. 1981; Healy et al. 1982; Schwetz et al. 1975).

Oral studies in animals exposed during gestation only or gestation and postnatal development include reports of trichloroethylene-induced decreased litter size and micro- or anophthalmia (Narotsky and Kavlock 1995; Narotsky et al. 1995), increased perinatal mortality (Manson et al. 1984; NTP 1985), increased incidences of fetal heart abnormalities (Dawson et al. 1993; Johnson et al. 1998, 2003), decreased numbers of myelinated fibers and other changes in the hippocampus (Blossom et al. 2012; Isaacson and Taylor 1989), decreased uptake of glucose by the brain (Noland-Gerbec et al. 1986), and behavioral changes (NTP 1986; Taylor et al. 1985). One study reported behavioral changes in mice exposed orally during postnatal days 10–16 only (Fredriksson et al. 1993). Recent studies assessed effects of trichloroethylene on the immune system of developing animals. Exposure of MRL+/+ mouse dams to trichloroethylene in the drinking water during gestation and lactation and continued exposure of the pups via the drinking water for an additional 4 weeks resulted in effects that included increased IFN-γ production by splenic CD4+ cells; decreased splenic CD+4, CD8+, and B220+ lymphocytes; increased

splenic CD4+ T-cell production of cytokines IFN-γ and IL-2 in females and TNF-α in males; and altered thymocyte profiles (Blossom and Doss 2007; Blossom et al. 2008). Another study noted a significantly decreased PFC response in male and female mouse pups and increased hypersensitivity response in male mouse pups exposed to trichloroethylene via their mothers during gestation and lactation and via their drinking water until they reached up to 8 weeks of age (Peden-Adams et al. 2006).

Further monitoring for birth defects in humans exposed to trichloroethylene are needed, especially in populations in which exposure concentrations could be determined.

Immunotoxicity. Immunological abnormalities (altered ratios of T-lymphocyte subpopulations, increased incidence of auto-antibodies, and increased infections) were noted in adults from 28 families exposed to trichloroethylene-contaminated well water. These families also had children with leukemia who had been exposed to trichloroethylene *in utero* (Byers et al. 1988). Isolated cases of dermal sensitivity and allergic responses in humans have been reported (Bauer and Rabens 1974; Conde-Salazar et al. 1983; Czirjak et al. 1993; Goh and Ng 1988; Nakayama et al. 1988; Phoon et al. 1984; Schattner and Malnick 1990; Waller et al. 1994). An increase in the symptoms of systemic lupus erythematosus has been reported in persons exposed to trichloroethylene in their drinking water (Kilburn and Warshaw 1992). Significantly lower total numbers of lymphocytes, T cells, CD4+ T cells, CD8+ T cells, B cells and NK cells were reported in trichloroethylene-exposed workers at factories in China that used trichloroethylene for cleaning a variety of materials and products (Lan et al. 2010). There is some evidence for an association between occupational exposure to trichloroethylene and the occurrence of scleroderma (Diot et al. 2002; EPA 2011e; Garabrant et al. 2003; Nietert et al. 1998).

Immunological end points have been studied to some extent in animals exposed to trichloroethylene; some assessments of the potential for trichloroethylene to accelerate autoimmune diseases employed strain of mice that spontaneously develop conditions resembling the human disease, systemic lupus erythematosus (SLE). A limited study in animals presents evidence for increased susceptibility to *S. zooepidomicus* (Aranyi et al. 1986). Immune system effects observed in mice exposed orally to trichloroethylene include inhibition of cell-mediated immunity, delayed type hypersensitivity, and inhibition of antibody-mediated immunity (Sanders et al. 1982). Female mice appeared to be more sensitive than male mice. Some studies of autoimmune-prone mice indicate that trichloroethylene can accelerate autoimmune responses (Cai et al. 2008; Gilbert et al. 1999; Griffin et al. 2000a, 2000b; Khan et al. 1995). Keil et al. (2009) reported decreased thymus weight and increased serum levels of IgG and selected autoantibodies in female MRL+/+ mice administered trichloroethylene in the drinking water for

up to 30 weeks, but there was no evidence that trichloroethylene accelerated the onset of autoimmune disease. Seo and coworkers (Kobayashi et al. 2010, 2012; Seo et al. 2008b, 2012) presented evidence of trichloroethylene-induced enhancement of allergic or hypersensitivity reactions in animals exposed by the oral route.

Additional human and animal studies are needed to better characterize the immunological effects of trichloroethylene and determine the potential for immunological effects among people exposed to trichloroethylene in the vicinity of hazardous waste sites.

Refer to Developmental Toxicity (above) for a summary of developmental immunotoxicity.

Neurotoxicity. Sufficient human information exists to identify the nervous system as a primary target for acute toxicity. In cases of acute accidental or intentional overexposure to trichloroethylene, neurological effects include euphoria, giddiness, lethargy, confusion, dizziness, headache, nausea, difficulty swallowing, facial effects that indicate possible trigeminal nerve damage (including sensation deficits, jaw weakness, increased blink reflex latency), which may be irreversible, memory deficits, and unconsciousness (Adamek and Krupiński 2007; Buxton and Hayward 1967; Carrieri et al. 2007; Clearfield 1970; Feldman 1970; Feldman et al. 1985; James 1963; Lawrence and Partyka 1981; Lachnit and Pietschmann 1960; Leandri et al. 1995; Longley and Jones 1963; Milby 1968; Miller et al. 2002; Pembleton 1974; Thierstein et al. 1960; Troutman 1988). At one time, trichloroethylene was used as a surgical anesthetic in humans (Brittain 1948). Occupational studies show that workers also had neurological complaints such as dizziness and headaches (Bardodej and Vyskocil 1956; Barret et al. 1987; Buxton and Hayward 1967; Cavanagh and Buxton 1989; El Ghawabi et al. 1973; Grandjean et al. 1955; Lawrence and Partyka 1981; McCunney 1988; Nomiyama and Nomiyama 1977) as well as residual cranial nerve damage in some cases for which the exposure concentration or duration was generally greater (Barret et al. 1987; Buxton and Hayward 1967; Cavanagh and Buxton 1989; Feldman 1970; McCunney 1988; Ruijten et al. 1991).

Among persons known to have ingested large amounts of trichloroethylene, observed symptoms included muscle weakness, general motor restlessness, tremor, delirium, and coma (Liotier et al. 2008; Moritz et al. 2000; Morreale 1976; Perbellini et al. 1991; Stephens 1945; Todd 1954). Several studies of the population in Woburn, Massachusetts, exposed to trichloroethylene (along with other contaminants) in the drinking water did not reveal increases in neurological complaints (Byers et al. 1988; Lagakos et al. 1986b), but one study found possible residual cranial nerve damage when comparing the exposed and

nonexposed population cohorts (Feldman et al. 1988). Among persons in the ATSDR exposure subregistry, a statistically significant increase in impairment of hearing was reported in children <10 years of age at baseline assessment, but not at several follow-up timepoints (ATSDR 1994, 1999, 2002; Burg and Gist 1999; Burg et al. 1995; Davis et al. 2005).

In a study that assessed possible associations between exposure to solvents and risk of Parkinson's disease, ever exposure to trichloroethylene was associated with a significantly increased risk (Goldman et al. 2012).

Acute exposure via the inhalation route results in adverse central nervous system effects in animals, as indicated by quicker fatigue when rats were placed in a tank of water with weights loaded to their tails (Grandjean 1963). The shuttle box or maze performances of these rats were not affected by the exposure. Other inhalation studies in animals include reported behavioral changes (Albee et al. 1993; Arito et al. 1994a; Battig and Grandjean 1963; Bushnell 1997; Bushnell and Oshiro 2000; Goldberg et al. 1964a; Kulig 1987; Silverman and Williams 1975; Waseem et al. 2001), biochemical and histopathological alterations (Haglid et al. 1981; Savolainen et al. 1977), and impaired hearing and vision (Albee et al. 1993, 2006; Blain et al. 1992, 1994; Boyes et al. 2000, 2003, 2005; Crofton and Zhao 1993, 1997; Crofton et al. 1994; Fechter et al. 1998; Jaspers et al. 1993; Kulig 1987; Muijser et al. 2000; Rebert et al. 1991).

Oral studies in animals include reports of trichloroethylene-induced neurological effects that include altered behavior (Moser et al. 1995; Narotsky et al. 1995; NTP 1988), increased foot splay (Nunes et al. 2001), and histopathological changes in the central nervous system (Barret et al. 1992; Gash et al. 2008; Henschler et al. 1984; Isaacson et al. 1990).

Application of a complete battery of neurological tests in animals exposed to trichloroethylene via the oral pathway is needed, although available data indicate that large oral doses are required to elicit neurological effects in animals. Neurological testing of humans with documented oral exposure to trichloroethylene could provide valuable insight as well.

Epidemiological and Human Dosimetry Studies. The epidemiological data for inhalation exposure to trichloroethylene derives from exposure in the workplace or intentional overexposure by inhalation. Many of the studies do not include adequate characterization of exposure levels and associated health effects. Epidemiological data for oral exposure to trichloroethylene are predominantly

available from studies of trichloroethylene in the drinking water where trichloroethylene has been associated with cardiovascular effects, dermal effects, immunological effects, neurological effects, increased incidences of selected birth defects, and cancer. The greatest limitations of most epidemiological studies are the difficulty in estimating dose and exposure to multiple chemicals. Additional epidemiological studies are needed that focus on the effects of low levels of trichloroethylene in the air, water, or soil near hazardous waste sites. These studies should carefully consider possible confounding factors including exposure to multiple chemicals, smoking and drinking habits, age, and gender. The end points that need to be carefully considered are kidney and liver effects, cardiovascular effects, developmental effects, neurological effects, immunological effects, and cancer.

Biomarkers of Exposure and Effect

Exposure. There is a large body of literature concerning the measurement of trichloroethylene in the breath and its principal metabolites (TCA, trichloroethanol, and trichloroethanol glucuronide) in the urine and blood (Csanády et al. 2010; Ertle et al. 1972; Ikeda et al. 1972; Imamura and Ikeda 1973; Imbriani et al. 2001; Kimmerle and Eben 1973b; Monster et al. 1979; Müller et al. 1972, 1974, 1975; Nomiyama 1971; Nomiyama and Nomiyama 1977; Ogata et al. 1971; Skender et al. 1993; Stewart et al. 1970; Vartiainen et al. 1993). However, there is a high degree of variation among individuals, so these methods should be used with caution for determining exposure levels. ACGIH has developed BEIs for trichloroethylene metabolites in urine (TCA, trichloroethanol) and blood (trichloroethanol) (ACGIH 2012).

Effect. Reliable biomarkers of effects are not available for trichloroethylene. There is no clinical disease state that is unique to trichloroethylene exposure. Interpretation of the behavioral observations in humans is complicated by many factors, such as possible irritant effects of the odor and nonspecific effects on the nervous system (e.g., fatigue). Further studies in this area would be useful in determining the exposure levels that may be associated with adverse effects in exposed populations. There is also a need to further explore the use of blink reflex latency as a marker for possible cranial nerve damage. This method has proven useful in detecting differences between exposed and nonexposed groups of people, but further refinement of the method is needed for its use in individual assessment. A limited number of studies of workers occupationally exposed to trichloroethylene for chronic periods have reported increases in serum levels of liver enzymes (Bauer and Rabens 1974; Schuttmann 1970), liver enlargement (Schuttmann 1970), and increased urinary NAG activity (Brogren et al. 1986). Although these effects are not specific

for trichloroethylene exposure, additional research further defining dose-response relationships for these effects would be useful.

Absorption, Distribution, Metabolism, and Excretion. There are some gaps in the current literature concerning information on the pharmacokinetics of trichloroethylene in humans and animals. Inhalation and oral absorption data for trichloroethylene in humans are based largely on poisoning cases, and no actual rates of absorption are available (Astrand and Ovrum 1976; Fernandez et al. 1977; Kleinfeld and Tabershaw 1954; Sato and Nakajima 1978). Dermal absorption studies of trichloroethylene dissolved in water (as a vehicle) are lacking, and studies using pure liquid trichloroethylene to measure dermal absorption are complicated by the fact that trichloroethylene defats the skin and enhances its own absorption. Data on the distribution of trichloroethylene in humans and animals are very limited, although the systemic distribution of trichloroethylene has been extensively studied in animals. Several investigators are working on PBPK models of trichloroethylene distribution in animals, and studies are underway to compare the differences in distribution of trichloroethylene following oral and inhalation exposure in rats. Some new metabolites of trichloroethylene in humans and animals have been reported in the recent literature, but these reports are still awaiting confirmation. Saturation of metabolism has been postulated to occur in humans, but few experimental data are available (Feingold and Holaday 1977). In animals, there are species differences in concentrations at which trichloroethylene metabolism becomes saturated, with mice reaching saturation at higher concentrations than rats (Dallas et al. 1991; Dekant et al. 1986b; Filser and Bolt 1979; Prout et al. 1985). Thus, the blood of mice can be found to contain greater concentrations of toxic metabolites, which are hypothesized to lead to induction of hepatocellular carcinoma in mice exposed to trichloroethylene (Fisher et al. 1991; Larson and Bull 1992b). Additional data clarifying the rate of absorption, the distribution, and the metabolism of trichloroethylene in humans would be useful.

Comparative Toxicokinetics. In humans, the targets for trichloroethylene toxicity are the liver, kidney, cardiovascular system, and nervous system. Experimental animal studies support this conclusion, although the susceptibilities of some targets, such as the liver, appear to differ between rats and mice. The fact that these two species could exhibit such different effects allows us to question which species is an appropriate model for humans. A similar situation occurred in the cancer studies, where results in rats and mice had different outcomes. The critical issue appears to be differences in metabolism of trichloroethylene across species (Andersen et al. 1980; Buben and O'Flaherty 1985; Filser and Bolt 1979; Prout et al. 1985; Stott et al. 1982). Further studies relating the metabolism of humans to those of rats and mice are needed to confirm the basis for differences in species and sex susceptibility to trichloroethylene's

toxic effects and in estimating human health effects from animal data. PBPK models have been developed to estimate human health effects from animal data and to estimate effects across exposure routes (see Section 3.4.5 for descriptions of PBPK models for trichloroethylene).

Methods for Reducing Toxic Effects. The general recommendations for reducing the absorption of trichloroethylene following acute inhalation, oral, dermal, or ocular exposure are well established and have a proven efficacy (D'Souza et al. 1985; HSDB 2013; Withey et al. 1983). No additional investigations are considered necessary at this time.

No clinical treatments other than supportive measures are currently available to enhance elimination of trichloroethylene following exposure. Studies designed to assess the potential risks or benefits of increasing ventilation to enhance pulmonary elimination or of stimulating excretion of trichloroethylene and its decomposition products are needed.

The mechanism of action for liver toxicity and carcinogenicity may involve the formation of reactive products (Bonse and Henschler 1976; Bonse et al. 1975; Fisher et al. 1991; Larson and Bull 1992b). Methods for reducing the destructive damage caused by these intermediates, or for blocking their formation through inhibition of metabolic pathways, may prove effective in reducing hepatic toxicity, but are not currently available for clinical use.

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

Intake from trichloroethylene-contaminated drinking water is expected to be greater in children than adults because children tend to drink more water on a per kg bodyweight basis than adults. Nursing infants can be exposed to trichloroethylene via the breast milk (Pellizzari et al. 1982). Household dust and dirt are potential sources of greater potential dermal contact and ingestion exposure in small children, although no information was located regarding trichloroethylene levels in household dust or dirt. Trichloroethylene intake from the ambient air is expected to be greater in infants and children than adults because infants and children have increased ventilation rates per kilogram body weight and alveolar surface area is 2-fold higher in infants compared to adults (EPA 2008). Trichloroethylene is lipophilic and distributes to all body tissues (see Section 3.4.2). At comparable absorption levels, such lipophilic substances may become more concentrated in the fat of infants and small children due to their lower amounts of fat per kilogram

body weight compared to adolescents and adults (NRC 1993). Trichloroethylene crosses the blood-brain barrier, and the extent of transfer could possibly be greater in young children, although trichloroethylene is expected to readily cross the blood-brain barrier in all age groups. Age-related differences in trichloroethylene metabolism could result in differences in susceptibility to trichloroethylene toxicity.

Additional human and animal studies are needed to assess whether infants and children are more susceptible than adults to trichloroethylene toxicity.

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

3.12.3 Ongoing Studies

Under the auspices of ATSDR's Voluntary Research Program (VPR), the Halogenated Solvents Industry Alliance (HSIA) has planned to study PBPK dose route conversion for immunological effects described in a rat inhalation study (Boverhof et al. 2013). The HSIA has also planned an oral developmental neurotoxicity study in rats. These studies are designed to address priority data needs identified by ATSDR (2011a) and as cited in the Federal Register (FR Doc. 05-23361; FR Doc. 96-7852).

Other ongoing studies pertaining to trichloroethylene have been identified and are shown in Table 3-12.

Table 3-12. Ongoing Studies on Trichloroethylene

Principal investigator	Study topic	Institution	Sponsor
Blossom, SJ	CD4+ T cell-mediated neurotoxicity with continuous trichloroethylene exposure	Arkansas Children's Hospital Research Institute, Little Rock, Arkansas	National Institute of Environmental Health Sciences
Khan, MF	Trichloroethylene exposure and autoimmune hepatitis	University of Texas, Galveston, Texas	National Institute of Environmental Health Sciences
Loch-Caruso, RK	Mechanisms of action related to risk of preterm birth and other adverse birth outcomes associated with environmental contaminants	Northeastern University, Boston, Massachusetts	National Institute of Environmental Health Sciences

PBPK = physiologically-based pharmacokinetic

Source: RePORTER 2018

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4. CHEMICAL AND PHYSICAL INFORMATION

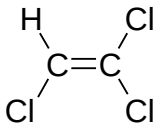
4.1 CHEMICAL IDENTITY

The chemical formula, structure, synonyms, and identification numbers for trichloroethylene are listed in Table 4-1.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Important physical and chemical properties of trichloroethylene are listed in Table 4-2.

Table 4-1. Chemical Identity of Trichloroethylene

Characteristic	Information	
Chemical name	Trichloroethylene	
Synonym(s)	Acetylene trichloride; 1-chloro-2,2-dichloroethylene; 1,1-dichloro-2-chloroethylene; ethylene trichloride; TCE; 1,1,2-trichloroethylene; trichloroethene	CAS 2011; ChemIDplus 2013
Registered trade name(s)	Algylen; Anamenth; Benzinol; Blancosolv; Cecolene; Chlorilen; Chlorylen; Densinfluat; Dow-tri; Fleck-flip; Flock FLIP; Fluate; Germalgene; Lanadin; Lethurin; Narcogen; Narkosoid; Nialk; Perm-A-chlor; Petzinol; Philex; Threthylen; Threthylene; Trethylene; Tri; Triasol; Trichloran; Trichloren; Triclene; Trielene; Trielin; Trieline; Trilen; Trilene; Trimar; Vestrol; Vitran; Westrosol	ChemIDplus 2013; IARC 1995
Chemical formula	C_2HCl_3	ChemIDplus 2013
Chemical structure		ChemIDplus 2013
Identification numbers:		
CAS registry	79-01-6	ChemIDplus 2013
NIOSH RTECS	KX4550000	NIOSH 2011
EPA hazardous waste	U228; F002; D040	HSDB 2013
DOT/UN/NA/IMDG shipping	UN1710; IMO6.1	HSDB 2013
HSDB	133	HSDB 2013
NCI	NCI-C04546	HSDB 2013

CAS = Chemical Abstracts Service; DOT/UN/NA/IMDG = 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; RTECS = Registry of Toxic Effects of Chemical Substances

Table 4-2. Physical and Chemical Properties of Trichloroethylene[a]

Property	Information
Molecular weight	131.39
Color	Clear, colorless
Physical state	Liquid
Melting point	-84.7°C
Boiling point	87.2°C
Density at 20°C	1.4642 g/cm^3
Vapor density (air=1)	4.53
Odor	Ethereal; chloroform-like; sweet
Odor threshold:	
Water	No data
Air	21.4 ppm
Solubility:	
Water at 25°C	1,280 mg/L[b]
Organic solvents	Soluble in ethanol, diethyl ether, acetone, and chloroform
Partition coefficients:	
Log K_{ow}	2.61
Log K_{oc}	49–460[c]
Vapor pressure at 20°C	69 mm Hg at 25°C[d]
Henry's law constant at 25°C	9.85x10^{-3} atm-m^3/mol at 25°C[e]
Autoignition temperature	420°C
Flashpoint	No data
Flammability limits	8.0–10.5%
Conversion factors	1 mg/m^3=0.18 ppm[f] 1 ppm=5.46 mg/m^3 [f]
Explosive limits	No data

[a]All information obtained from HSDB 2013, except where noted.
[b]Horvath et al. 1999.
[c]Brigmon et al. 1998; Chiou and Kile 1998; Garbarini and Lion 1986; Mouvet 1993; Rathbun 1998; Sahoo and Smith 1997.
[d]Boublik et al. 1984.
[e]Leighton and Calo 1981.
[f]Calculated based on molecular weight.

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

5.1 PRODUCTION

Trichloroethylene is currently produced in the United States using ethylene dichloride (a product of ethylene and chlorine feedstocks) (CMR 2005; EPA 1985e; Rossberg 2006; Snedecor et al. 2004). PPG Industries uses a single-step oxychlorination process, which yields trichloroethylene and tetrachloroethylene. In the PPG process, ethylene dichloride is reacted with chlorine and/or hydrogen chloride and oxygen to form the trichloroethylene and tetrachloroethylene. DOW Chemical produces trichloroethylene by a direct chlorination process, in which ethylene dichloride is reacted with chlorine to form trichloroethylene and tetrachloroethylene. Use of acetylene as a feedstock for trichloroethylene production declined significantly during the 1970s, and this method is no longer used (Rossberg 2006; Snedecor et al. 2004).

The production volume of trichloroethylene in the United States was reported to be 354 million pounds in 1960, 612 million pounds in 1970, 267 million pounds in 1980, and 195 million pounds in 1987 (Mertens 2000). The U.S. production demand was 165 million pounds in 1993, 192 million pounds in 2000, and 218 million pounds in 2004 (CMR 1989, 2005). According to the U.S. EPA Inventory Update Reporting database, the annual production of trichloroethylene during 2006 was between 100 and 500 million pounds (EPA 2010a). More recent production data for trichloroethane have not been located. According to the EPA Chemical Data Reporting rule, there were nine domestic manufacturers of trichloroethylene in 2012, with a national production volume of 224,674,308 pounds per year (EPA 2015a).

Table 5-1 summarizes the number of facilities in each state that manufactured or processed trichloroethylene in 2017, the ranges of maximum amounts on site, if reported, and the activities and uses as reported in the Toxics Release Inventory (TRI) (TRI17 2018). The data listed in this table should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list.

5.2 IMPORT/EXPORT

As a result of the strength of the U.S. dollar in foreign markets, imports of trichloroethylene rose steadily from 8 million pounds in 1980 to 40 million pounds in 1985 (CMR 1986). During the same time period, exports of trichloroethylene fell from 60 million pounds to 18 million pounds. Reported U.S. imports

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

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AL	3	1,000	99,999	12
AR	2	100	999,999	12
AZ	2	1,000	99,999	12
CA	2	1,000	99,999	7,12
CO	1	10,000	99,999	12
CT	4	1,000	999,999	9,12
DE	1	10,000	99,999	12
GA	8	1,000	999,999	7,9,12
IA	1	1,000	9,999	11
IL	15	1,000	99,999	1,2,3,4,6,7,9,10,11,12
IN	4	1,000	999,999	9,11,12,14
KS	6	100	99,999	1,5,7,10,11,12
KY	6	100	9,999,999	1,3,6,9,12
LA	14	0	49,999,999	1,3,4,5,6,12,13,14
MA	5	1,000	49,999,999	7,9,12
ME	1	1,000	9,999	11
MI	2	1,000	9,999	7,11
MN	7	1,000	99,999	6,10,12
MO	8	1,000	99,999	2,3,7,9,11,12
NE	2	10,000	999,999	9,12
NJ	2	1,000	999,999	7,9,12
NM	1	10,000	99,999	12
NV	1	10,000	99,999	7
NY	3	100	9,999	12
OH	13	1,000	999,999	7,10,12
OK	1	1,000	9,999	12
OR	2	10,000	999,999	11,12
PA	9	1,000	999,999	7,9,11,12
SC	4	100	999,999	6,12
TN	3	10,000	99,999	10,12
TX	10	1,000	499,999,999	1,3,4,5,6,7,9,12,13,14
UT	3	100	999,999	11,12
VA	2	1,000	99,999	7,11
VT	1	1,000	9,999	12
WA	1	100	999	6,7,12

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

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
WI	3	1,000	99,999	7,9,11,12
WV	1	0	0	0

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

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

Source: TRI17 2018 (Data are from 2017)

during the years 2000, 2002, and 2004 were 10, 19, and 20 million pounds, respectively (CMR 2005). Reported U.S. exports during these same 3 years were 76, 52, and 55 million pounds, respectively (CMR 2005). The continued strength of U.S. exports during this time period was most likely due to the high global demand for trichloroethylene as a feedstock for the refrigerant HFC-134a (CMR 2002, 2005; Snedecor et al. 2004). More recent data regarding US imports and exports of trichloroethylene have not been located.

5.3 USE

The end-use pattern of trichloroethylene in the United States during 2004 was estimated as follows (CMR 2005): hydrofluorocarbon (HFC-134a) intermediate, 73%; metal degreasing, 24%; and miscellaneous uses, 3%. Historically, the most important use of trichloroethylene has been vapor degreasing of metal parts, which is closely associated with the automotive and metals industries (CMR 1983). This use has declined over the past decade due to increased environmental regulations governing trichloroethylene emissions (CMR 2000, 2002, 2005). During the same time period, trichloroethylene found increasing use as a feedstock for HFC-134a, a refrigerant that was introduced as a replacement for CFC-12 during the 1990s (CMR 1995, 1997, 2000, 2002, 2005; Snedecor et al. 2004).

Trichloroethylene is an excellent extraction solvent for greases, oils, fats, waxes, and tars and has been used by the textile processing industry to scour cotton, wool, and other fabrics (Bakke et al. 2007; IARC 1979; ACS 1986; Verschueren 1983). The textile industry has also used trichloroethylene as a solvent in waterless drying and finishing operations (Bakke et al. 2007; McNeill 1979; Snedecor et al. 2004). As a general solvent or as a component of solvent blends, trichloroethylene has been used with adhesives, lubricants, paints, varnishes, paint strippers, pesticides, and cold metal cleaners (Bakke et al. 2007; IARC 1979; McNeill 1979; PPG 2005).

Trichloroethane has had widespread use as a chain transfer agent in the production of polyvinyl chloride (PVC) (CMR 2005; PPG 2005; Snedecor et al. 2004). Other chemical intermediate uses of trichloro-ethylene have included production of pharmaceuticals, polychlorinated aliphatics, flame retardant chemicals, and insecticides (Bakke et al. 2007; Windholz 1983). Trichloroethylene is used as a refrigerant for low-temperature heat transfer (Cooper and Hickman 1982; IARC 1979; McNeill 1979; Snedecor et al. 2004) and in the aerospace industry for flushing liquid oxygen (PPG 2005).

Prior to 1977, trichloroethylene was used as a general and obstetrical anesthetic; grain fumigant; skin, wound, and surgical disinfectant; pet food additive; and extractant of spice oleoresins in food and of caffeine for the production of decaffeinated coffee. These uses were banned by a U.S. Food and Drug Administration (FDA) regulation promulgated in 1977 (IARC 1979; Snedecor et al. 2004).

5.4 DISPOSAL

The recommended method of trichloroethylene disposal is incineration after mixing with a combustible fuel (Sittig 1985). Care should be taken to carry out combustion to completion in order to prevent the formation of phosgene (Sjoberg 1952). Other toxic byproducts of incomplete combustion include polycyclic aromatic hydrocarbons and perchloroaromatics (Blankenship et al. 1994; Mulholland et al. 1992). An acid scrubber also must be used to remove the haloacids produced.

According to EPA regulations, land disposal of halogenated organic solvents (such as trichloroethylene) is restricted (EPA 1987e). Before land disposal of trichloroethylene or trichloroethylene-containing materials is attempted, proper authorization must be obtained from federal, state, and local authorities.

There has been an emphasis on recovery and recycling of trichloroethylene to reduce emissions of this photoreactive chemical to the atmosphere (CMR 2002; McNeill 1979; Snedecor et al. 2004). Photooxidative destruction has been successfully used in conjunction with air-stripping techniques to volatilize trichloroethylene from water and degrade it to nontoxic products (Bhowmick and Semmens 1994). If possible, recycling should be used instead of disposal.

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6. POTENTIAL FOR HUMAN EXPOSURE

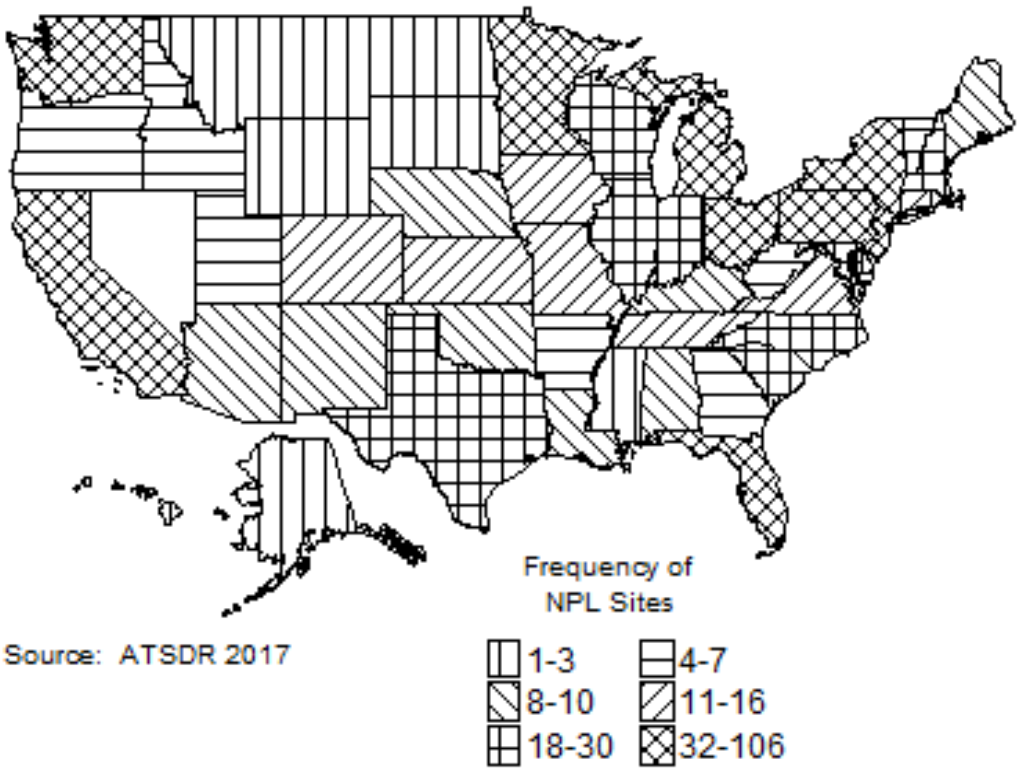
6.1 OVERVIEW

Trichloroethylene has been identified in at least 1,051 of the 1,854 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2017a). However, the number of sites evaluated for trichloroethylene is not known. The frequency of these sites can be seen in Figure 6-1. Of these sites, 1,043 are located within the United States, 1 is located in Guam, 1 is located in the Virgin Islands, and 6 are located in Puerto Rico (not shown).

Most of the trichloroethylene used in the United States is released into the atmosphere by evaporation primarily from degreasing operations. Once in the atmosphere, the dominant trichloroethylene degradation process is reaction with hydroxyl radicals; the estimated half-life for this process is approximately 7 days. This relatively short half-life indicates that trichloroethylene is not a persistent atmospheric compound. Most trichloroethylene deposited in surface waters or on soil surfaces volatilizes into the atmosphere, although its high mobility in soil may result in substantial percolation to subsurface regions before volatilization can occur. In these subsurface environments, trichloroethylene is only slowly degraded and may be relatively persistent. Trichloroethylene and other volatile organic chemicals may off-gas from contaminated groundwater and soil and migrate into air spaces beneath buildings to enter the indoor air, a process termed vapor intrusion (EPA 2002).

In general, atmospheric levels are highest in areas of concentrated industry and population and lower in rural and remote regions. Mean trichloroethylene concentrations measured in air at locations across the United States are generally between 0.01 and 0.3 ppb, although mean levels as high as 3.4 ppb have been reported (EPA 2011f). Workers, particularly in the degreasing industry, are exposed by inhalation to the highest levels of trichloroethylene. Based upon monitoring surveys, these workers may be exposed to levels ranging from approximately 1 to 100 ppm. The general population can also be exposed to trichloroethylene by contact with and/or consumption of water from supplies contaminated with the chemical, by consumption of contaminated foods, and by contact with consumer products containing the compound. Between 4.5 and 18% of the drinking water supply sources in the United States that are tested on a yearly basis by the U.S. EPA have some trichloroethylene contamination. Levels are typically <30 ppb. Trichloroethylene levels in the low ppb range have been measured in food; however, levels as high as 140 ppb were measured in a few samples. It should be noted that the amount of trichloroethylene found by chemical analysis is not necessarily the amount that is bioavailable.

Figure 6-1. Frequency of NPL Sites with Trichloroethylene Contamination



Source: ATSDR 2017

6.2 RELEASES TO THE ENVIRONMENT

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

6.2.1 Air

Estimated releases of 1,886,809 pounds (855.8 metric tons) of trichloroethylene to the atmosphere from 154 domestic manufacturing and processing facilities in 2017, accounted for about 92% of the estimated total environmental releases from facilities required to report to the TRI (TRI17 2018). These releases are summarized in Table 6-1.

In a comprehensive study of trichloroethylene emission sources from industry conducted for EPA, the major source was degreasing operations, which eventually release most of the trichloroethylene used in this application to the atmosphere (EPA 1985e). Degreasing operations represented the largest source category of trichloroethylene emissions in 1983, accounting for about 91% of total trichloroethylene emissions. Other emission sources include relatively minor releases from trichloroethylene manufacture, manufacture of other chemicals (similar chlorinated hydrocarbons and polyvinyl chloride), and solvent evaporation losses from adhesives, paints, coatings, and miscellaneous uses. Millet et al. (2009) estimated a trichloroethylene emission rate of 7.6 Gg/year (7,600 metric tons/year) based on aircraft measurements collected over the United States from 2004 to 2006.

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Trichloroethylene[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
AL	3	99,952	0	0	0	780	99,952	780	100,732
AR	2	59	0	0	0	11	59	11	70
AZ	2	10,483	0	0	250	0	10,483	250	10,733
CA	2	45	0	0	0	0	45	No data	45
CO	1	6,560	0	0	0	0	6,560	No data	6,560
CT	4	56,090	0	0	0	0	56,090	No data	56,090
DE	1	1,275	0	0	0	0	1,275	No data	1,275
GA	8	17,005	0	0	0	0	17,005	No data	17,005
IA	1	10,306	0	0	0	0	10,306	No data	10,306
IL	15	98,618	0	0	5	2,013	98,618	2,018	100,636
IN	4	716,301	5	3,349	715	0	716,306	4,064	720,370
KS	6	106,509	1	374	306	116	106,884	422	107,306
KY	6	31,718	26	0	0	0	31,744	No data	31,744
LA	14	50,948	2	0	11	1,028	50,950	1,039	51,989
MA	5	28,747	0	0	0	1,436	28,747	1,436	30,183
ME	1	3,413	0	0	0	2,058	3,413	2,058	5,471
MI	2	11,581	0	0	0	0	11,581	No data	11,581
MN	7	81,337	0	0	0	0	81,337	No data	81,337
MS	8	39,902	0	0	0	0	39,902	No data	39,902
NE	2	28,119	0	0	632	0	28,119	632	28,751
NJ	2	8,898	0	0	0	0	8,898	No data	8,898
NM	1	118	0	0	90,876	0	90,994	No data	90,994
NV	1	500	0	0	0	0	500	No data	500
NY	3	7,498	0	0	0	0	7,498	No data	7,498
OH	13	101,363	0	0	0	27,570	101,363	27,571	128,934
OK	1	426	0	0	0	0	426	No data	426
OR	2	56,282	0	0	22,917	0	79,199	No data	79,199
PA	9	168,860	0	0	31	77	168,860	109	168,968
SC	4	5,444	0	0	0	0	5,444	No data	5,444
TN	3	113,282	0	0	0	0	113,282	No data	113,282
TX	10	4,444	0	0	38	324	4,444	362	4,806
UT	3	8,421	0	0	11	0	8,421	11	8,432
VA	2	1,962	0	0	0	0	1,962	No data	1,962
VT	1	11	0	0	0	0	11	No data	11

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Trichloroethylene[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
WA	1	1,980	0	0	0	0	1,980	No data	1,980
WI	3	8,353	0	0	0	0	8,353	No data	8,353
Total	154	1,886,809	34	3,723	115,793	35415	2,001,010	40,764	2,041,774

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

RF = reporting facilities; UI = underground injection

Source: TRI17 2018 (Data are from 2017)

More recent data continue to suggest that degreasing operations represent the greatest emission source of trichloroethylene to the atmosphere; however, levels have been significantly reduced in the past 2 decades as new engineering controls and design features in degreasing operations have been initiated under the National Emissions Standard for Hazardous Air Pollutants (NESHAP), which limits emissions from degreasers using traditional solvents like trichloroethylene. Section 112(b) of the Clean Air Act (CAA) lists trichloroethylene as one of 188 hazardous air pollutants (HAPs) known to cause or suspected of causing cancer or other serious human health effects or ecosystem damage (EPA 2000). EPA's National Emission Inventory (NEI) database contains data regarding sources that emit criteria air pollutants and their precursors, and HAPs for the 50 United States, Washington DC, Puerto Rico, and the U.S. Virgin Islands (prior to 1999, criteria pollutant emission estimates were maintained in the National Emission Trends [NET] database and HAP emission estimates were maintained in the National Toxics Inventory [NTI] database). The NEI database derives emission data from multiple sources, including state and local environmental agencies; the TRI database; computer models for on- and off-road emissions; and databases related to EPA's Maximum Achievable Control Technology (MACT) programs to reduce emissions of HAPs. Using composite data from the NTI database from 1990 to 1993, it was estimated that the annual emissions of trichloroethylene in the United States was approximately 71,999 tons per year during that time frame (EPA 2000). More recent data illustrate the decline in trichloroethylene emissions in the United States. Data downloaded from the 2005 NEI (see Table 6-2) indicated that the total emission of trichloroethylene was approximately 9,911 tons, with the largest contribution arising from non-point solvent degreasing sources (EPA 2011a). Data downloaded from the 2008 NEI (see Table 6-3) indicated that the total emission of trichloroethylene decreased to 3,692 tons, with approximately 75% of the total arising from solvent degreasing (EPA 2013b). Data from the 2011 NEI (see Table 6-4) showed a further decline in trichloroethylene emissions to approximately 3,250 tons (EPA 2015b).

A natural source of trichloroethylene is its production by several species of marine macroalgae and at least one species of marine microalgae (Abrahamsson et al. 1995). Rates of production ranged from 0.022 to 3,400 ng/g fresh weight/hour, with the higher rates seen in subtropical *Rhodophyta* species. The importance of this source of trichloroethylene could not be estimated due to the lack of knowledge of its production in other species of algae. Also not fully understood is the physiology of how trichloroethylene is produced and how environmental factors may affect its production rate. It is not known whether this source could be a potential concern as a major source of atmospheric emissions of trichloroethylene in coastal areas since there are many unknown factors. However, modeling of the distribution of

Table 6-2. 2005 NEI Total National Emissions

Source	Name	Annual emissions in tons
Nonpoint	Solvent; NEC	2,062.42
Nonpoint	Graphic arts	0.26
Nonpoint	Industrial process; NEC	5.43
Nonpoint	Industrial process; chemical manufacturing	0.10
Nonpoint	Fuel comb; commercial/institutional	0.01
Nonpoint	Indus process; metals	0.48
Nonpoint	Dry cleaning	346.96
Nonpoint	Solvent; non-industrial	241.64
Nonpoint	Surface coating; industrial	2.72
Nonpoint	Waste disposal	142.32
Nonpoint	Degreasing	2,645.34
Point	Degreasing	2,057.58
Point	Fuel comb; commercial/institutional	0.32
Point	Fuel comb; electric utility	0.71
Point	Fuel comb; industrial boilers, ICEs	1.35
Point	Graphic arts	4.99
Point	Dry cleaning	0.05
Point	Indus process; cement manufacturing	0.03
Point	Bulk gasoline terminals	0.00
Point	Indus process; metals	7.17
Point	Waste disposal; open burning	0.14
Point	Indus process; NEC	1,417.97
Point	Indus process; petroleum refineries	1.02
Point	Indus process; pulp and paper	37.71
Point	Indus process; storage and transfer	14.69
Point	Solvent; NEC	107.15
Point	Surface coating; industrial	283.28
Point	Waste disposal	500.29
Point	Indus process; chemical manufacturing	29.30
Total		9,911

ICE = internal combustion engine; NEC = not elsewhere classified

Source: EPA 2011a

Table 6-3. 2008 National Air Emissions for Trichloroethylene

Sector	Air emissions in tons
Agriculture; livestock waste	0.02
Bulk gasoline terminals	1.93
Commercial cooking	0.00
Dust; construction dust	0.00
Fuel comb; commercial/institutional; biomass	0.35
Fuel comb; commercial/institutional; natural gas	0.09
Fuel comb; commercial/institutional; oil	0.05
Fuel comb; commercial/institutional; other	0.15
Fuel comb; electric generation; biomass	1.06
Fuel comb; electric generation; coal	0.14
Fuel comb; electric generation; natural gas	0.01
Fuel comb; electric generation; oil	0.02
Fuel comb; electric generation; other	0.07
Fuel comb; industrial boilers, ICEs; biomass	5.07
Fuel comb; industrial boilers, ICEs; coal	0.04
Fuel comb; industrial boilers, ICEs; natural gas	56.47
Fuel comb; industrial boilers, ICEs; oil	0.43
Fuel comb; industrial boilers, ICEs; other	0.17
Gas stations	0.03
Industrial processes; cement manuf	0.06
Industrial processes; chemical manuf	20.58
Industrial processes; ferrous metals	2.33
Industrial processes; mining	0.01
Industrial processes; NEC	248.05
Industrial processes; non-ferrous metals	17.88
Industrial processes; petroleum refineries	8.75
Industrial processes; pulp and paper	28.65
Industrial processes; storage and transfer	15.22
Miscellaneous non-industrial NEC	0.00
Mobile; non-road equipment; diesel	0.33
Solvent; consumer and commercial solvent use	164.60
Solvent; degreasing	2,781.51
Solvent; dry cleaning	0.07
Solvent; graphic arts	7.06
Solvent; industrial surface coating and solvent use	197.43
Waste disposal	133.18
Total	3,692

ICE = internal combustion engine; NEC = not elsewhere classified

Source: EPA 2013b

Table 6-4. 2011 National Air Emissions for Trichloroethylene

Sector	Air emissions in tons
Agriculture; livestock waste	0.002
Bulk gasoline terminals	0.04
Fuel comb; commercial/institutional; biomass	0.15
Fuel comb; commercial/institutional; natural gas	0.00009
Fuel comb; commercial/institutional; oil	0.0005
Fuel comb; commercial/institutional; other	0.16
Fuel comb; electric generation; biomass	1.28
Fuel comb; electric generation; coal	0.16
Fuel comb; electric generation; natural gas	0.09
Fuel comb; electric generation; oil	0.02
Fuel comb; electric generation; other	0.23
Fuel comb; industrial boilers, ICEs; biomass	5.6
Fuel comb; industrial boilers, ICEs; coal	0.07
Fuel comb; industrial boilers, ICEs; natural gas	1.74
Fuel comb; industrial boilers, ICEs; oil	0.043
Fuel comb; industrial boilers, ICEs; other	0.08
Industrial processes; cement manuf	0.24
Industrial processes; chemical manuf	63.6
Industrial processes; ferrous metals	15.9
Industrial processes; NEC	386.3
Industrial processes; non-ferrous metals	55.08
Industrial processes; petroleum refineries	4.33
Industrial processes; pulp and paper	33.06
Industrial processes; storage and transfer	8.18
Solvent; consumer and commercial solvent use	365.8
Solvent; degreasing	2162.70
Solvent; dry cleaning	0.008
Solvent; graphic arts	8.35
Solvent; industrial surface coating and solvent use	136.29
Total	3,250

ICE = internal combustion engine; NEC = not elsewhere classified

Source: EPA 2015b

trichloroethylene releases in the global atmosphere suggested much lower levels than are actually observed in the southern hemisphere, far from areas of release, indicating that oceanic emissions may be important (Olaguer 2002).

Release of trichloroethylene also occurs at treatment and disposal sites. Water treatment facilities may release trichloroethylene from contaminated water through volatilization and air-stripping procedures (EPA 1985e). Trichloroethylene is also released to the atmosphere through gaseous emissions from landfills. The compound may occur as either an original contaminant or as a result of the decomposition of tetrachloroethylene. Trichloroethylene has also been detected in stack emissions from the incineration of municipal and hazardous waste (James et al. 1985; Oppelt 1987). Pratt et al. (2004) estimated that 87 metric tons of trichloroethylene were released from publicly owned treatment works located in the Minneapolis-St. Paul, Minnesota metropolitan area in 1999.

6.2.2 Water

Estimated releases of 34 pounds (0.02 metric tons) of trichloroethylene to surface water, waste water treatment sites (metals only), and publicly owned treatment works (POTWs) (metal and metal compounds) from 154 domestic manufacturing and processing facilities in 2017, accounted for <1% of the estimated total environmental releases from facilities required to report to the TRI (TRI17 2018). These releases are summarized in Table 6-1.

Trichloroethylene is released to aquatic systems from industrial discharges of waste water streams (EPA 1985c). Various monitoring studies nationwide have also found that trichloroethylene from landfill leachate can contaminate groundwater (DeWalle and Chian 1981; Kosson et al. 1985; Reinhard et al. 1984; Sabel and Clark 1984; Schultz and Kjeldsen 1986). In fact, trichloroethylene is the most frequently reported organic contaminant in groundwater (Bourg et al. 1992).

6.2.3 Soil

Estimated releases of 115,793 pounds (52.5 metric tons) of trichloroethylene to soils from 154 domestic manufacturing and processing facilities in 2017, accounted for about 5.7% of the estimated total environmental releases from facilities required to report to the TRI (TRI17 2018). An additional 3,723 pounds (1.7 metric tons), were released via Class I wells, Class II-V wells, and underground injection (TRI17 2018). These releases are summarized in Table 6-1.

Trichloroethylene can be released into the soil through industrial discharges into surface waters and through landfill leachate. EPA regulations now restrict the disposal of hazardous waste containing greater than or equal to 1,000 mg/kg halogenated organic compounds (such as trichloroethylene) in landfills (EPA 1987e).

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

The relatively short predicted half-life of trichloroethylene in the atmosphere indicates that long-range global transport is unlikely (Class and Ballschmiter 1986). However, its constant release, as well as its role as an intermediate in tetrachloroethylene degradation, may account for its persistence and the fact that trichloroethylene is often present in remote areas.

Trichloroethylene has been detected in a number of rainwater samples collected in the United States and elsewhere (see Section 6.4.2). It is moderately soluble in water, and experimental data have shown that scavenging by rainwater occurs rapidly (Jung et al. 1992). Trichloroethylene can, however, be expected to revolatilize back to the atmosphere after being deposited by wet deposition. Evaporation from dry surfaces can also be predicted from the high vapor pressure.

The Henry's law constant value of 9.85×10^{-3} atm-m^3/mol at 25°C suggests that trichloroethylene partitions rapidly to the atmosphere from surface water. The major route of removal of trichloroethylene from water is volatilization (EPA 1985c). Laboratory studies have demonstrated that trichloroethylene volatilizes rapidly from water (Chodola et al. 1989; Dilling 1977; Okouchi 1986; Roberts and Dandliker 1983). Dilling et al. (1975) reported the experimental half-life with respect to volatilization of 1 mg/L trichloroethylene from water to be an average of 21 minutes at approximately 25°C in an open container. Although volatilization is rapid, actual volatilization rates are dependent upon temperature, water movement and depth, associated air movement, and other factors. A mathematical model based on Fick's diffusion law has been developed to describe trichloroethylene volatilization from quiescent water, and the rate constant was found to be inversely proportional to the square of the water depth (Peng et al. 1994).

Based on the measured Henry's law constant, the estimated volatilization half-life of trichloroethylene is 1.2 hours from a model river (1 meter deep, flowing 1 meter per second, with a wind velocity of 5 meters per second) and 4.6 days from a model lake (1 meter deep, flowing 0.05 meters per second, with a wind

velocity of 0.5 meters per second) (EPA 2010b). Measured volatilization half-lives in a mesocosm, which simulated the Narragansett Bay in Rhode Island during winter, spring, and summer, ranged from 13 days in summer conditions to 28 days in spring conditions (Wakeham et al. 1983).

Volatilization of trichloroethylene from soil is slower than it is from water, but is more rapid than that of many other volatile organic compounds (Park et al. 1988). This study found that an average of 37% of the applied trichloroethylene was volatilized 168 hours after treatment at 12°C, and 45% was volatilized at 21°C. This study also concluded that soil type had no effect on rate of volatilization, although this may simply be a reflection of the fact that the differences between soils used in the study, particularly in organic carbon content, were not very great.

Sorption of organic compounds to soil has been found to be most reliably predicted when related to the organic carbon content of the soil (Kenaga 1980; Urano and Murata 1985). Experimentally measured soil organic carbon sorption coefficients (K_{oc} values) for trichloroethylene generally range from 49 to 460 (Brigmon et al. 1998; Chiou and Kile 1998; Garbarini and Lion 1986; Mouvet 1993; Rathbun 1998; Sahoo and Smith 1997). The components of soil organic matter show widely varying affinities for trichloroethylene, with the fats-waxes-resins fraction being responsible for stronger adsorption of trichloroethylene (Garbarini and Lion 1986; Grathwohl 1990). The calculated K_{oc} values are indicative of medium-to-high mobility in soil (Kenaga 1980; Swann et al. 1983). Others have also shown that trichloroethylene is highly mobile in sandy soil (Wilson et al. 1981). Another study comparing predicted and observed sorption on clay and organic soils suggested that sorption/desorption to inorganic mineral surfaces may also play a role, and the reactions generally follow reversible pseudo first-order kinetics (Doust and Huang 1992).

Several models for describing the transport of volatile chlorinated hydrocarbons in soils have been developed, often by fitting one or more parameters to experimental data. One model that determined all parameters a priori and included transfer between solid, liquid, and gas phases found that the Henry's law constant was the primary determinant of transport behavior in a wet nonsorbing aggregated medium, suggesting that volatilization and movement in the gas phase accounts for a large portion of trichloroethylene movement in soils (Gimmi et al. 1993). However, as the velocities of the gas and liquid phases increase, equilibrium partitioning is less likely, and prediction from Henry's law is less reliable. This was found to be the case in laboratory and field experiments on trichloroethylene volatilization from contaminated groundwater and diffusion through soil (Cho et al. 1993). In addition, sorption of trichloroethylene to the surfaces of soil particles, which may decrease its transport and bioavailability, is

dependent on soil moisture content, since polar water molecules will compete aggressively with nonpolar vapor phase trichloroethylene for polar sorption sites. This has been experimentally confirmed with real soil samples, in which it was found that the solid/vapor partition coefficient decreased dramatically with increased moisture content (Petersen et al. 1994).

A number of groundwater monitoring studies have detected trichloroethylene in groundwater (see Section 6.4.2), which is further evidence of its leachability. The mobility of trichloroethylene in soil was demonstrated in a field study of river water infiltration to groundwater in which trichloroethylene was observed to leach rapidly into groundwater near sewage treatment plants in Switzerland (Schwarzenbach et al. 1983). No evidence of biological transformation of trichloroethylene in groundwater was found. Accurate prediction of trichloroethylene transport in groundwater is complicated by the sorption effect of organic and inorganic solids (Doust and Huang 1992).

Experimentally measured bioconcentration factors (BCFs), which provide an indication of the tendency of a chemical to partition to the fatty tissue of organisms, have been found to range between 10 and 100 for trichloroethylene in fish (Kawasaki 1980; Kenaga 1980; Neely et al. 1974; Veith et al. 1980). Barrows et al. (1980) estimated a value of 17 for bluegill sunfish. Somewhat lower BCFs were determined by Saisho et al. (1994) for blue mussel (4.52) and killifish (2.71). These numbers are suggestive of a low to moderate tendency to bioaccumulate.

Monitoring data on trichloroethylene concentrations in seawater and associated aquatic organisms are in agreement with the experimental BCF data. Concentrations of trichloroethylene (dry weight basis) detected in fish (eel, cod, coalfish, dogfish) from the relatively unpolluted Irish Sea ranged from below detection limits to 479 ppb (Dickson and Riley 1976). Levels of 2–56 ppb (wet weight) in liver tissue, and up to 11 ppb (wet weight) in other tissue, were found in various species of fish collected off the coast of Great Britain near several organochlorine plants (Pearson and McConnell 1975). Fish taken from the western coast of the United States near the discharge zone of the Los Angeles County waste-water treatment plant contained trichloroethylene levels of up to 6 ppb (wet weight) in liver tissue (Gossett et al. 1983). Clams and oysters from Lake Pontchartrain near New Orleans had trichloroethylene levels averaging between 0.8 and 5.7 ppb (wet weight) (Ferrario et al. 1985).

To assess bioaccumulation in the environment, the levels of trichloroethylene in the tissues of a wide range of organisms were determined (Pearson and McConnell 1975). Species were chosen to represent several trophic levels in the marine environment. The maximum overall increase in concentration

between sea water and the tissues of animals at the top of food chains, such as fish liver, sea bird eggs, and sea seal blubber, was <100-fold for trichloroethylene. Biomagnification in the aquatic food chain does not appear to be important (Pearson and McConnell 1975).

Trichloroethylene has also been detected in small amounts in fruits and vegetables, suggesting a potential for bioconcentration in plants (see Section 6.4.4), although some of the trichloroethylene may have been a result of exposure after harvesting. Laboratory studies with carrot and radish plants and radioactively labelled trichloroethylene revealed that uptake occurred mainly through the foliage as opposed to the roots in these plants, although subsequent translocation resulted in substantial distribution throughout the plants (Schroll et al. 1994). The study authors determined fairly moderate BCFs of between 4.4 and 63.9. Uptake of trichloroethylene in apple and peach trees and wheat, corn, and tomato seedlings has also been demonstrated (Chard et al. 2006; Doucette et al. 2007; Su et al. 2010).

6.3.2 Transformation and Degradation

6.3.2.1 Air

The dominant transformation process for trichloroethylene in the atmosphere is reaction with photochemically produced hydroxyl radicals (Singh et al. 1982). Using the recommended rate constant for this reaction at 25°C (2.36×10^{12} cm^3/molecule-second) and a typical atmospheric hydroxyl radical concentration (5×10^5 molecules/cm^3) (Atkinson 1985, 1989), the half-life can be estimated to be 6.8 days. Class and Ballschmiter (1986) state it as between 3 and 7 days.

The reaction of volatile chlorinated hydrocarbons with hydroxyl radicals is temperature dependent and thus varies with the seasons, although such variation in the atmospheric concentration of trichloroethylene may be minimal because of its brief residence time (EPA 1985c). The degradation products of this reaction include phosgene, dichloroacetyl chloride, and formyl chloride (Atkinson 1985; Gay et al. 1976; Kirchner et al. 1990). Reaction of trichloroethylene with ozone in the atmosphere is too slow to be an effective agent in trichloroethylene removal (Atkinson and Carter 1984).

6.3.2.2 Water

Oxidation of trichloroethylene in the aquatic environment does not appear to be a significant fate process, probably because of its having already been oxidized by the chlorine atoms. The rate of hydrolysis is also too slow to be an important transformation process (EPA 1979b). A study by Jensen and Rosenberg

(1975) indicated that the rate of volatilization of trichloroethylene proceeds more rapidly than photooxidation or hydrolysis. Studies of photolysis and hydrolysis conducted by Chodola et al. (1989) demonstrated that photolysis did not contribute substantially to the transformation of trichloroethylene. Chemical hydrolysis appeared to occur only at elevated temperature in a high pH environment and, even then, at a very slow rate. Studies of the degradation of trichloroethylene in water during ultraviolet irradiation indicated that degradation decreased with increases in the total organic content of the water (Beltran et al. 1995). In addition, the photolysis rate was found to increase when the initial concentration of trichloroethylene was low (Dobaradarane et al. 2012). The study also concluded that pH did not affect the photolysis rate of trichloroethylene.

Results from experiments conducted at high pH and temperature were extrapolated to pH 7 and 25°C (Jeffers et al. 1989), and the estimated half-life was $1.3x10^6$ years, which suggests that hydrolysis does not occur under normal environmental conditions. In contrast, estimates of the hydrolysis half-life of trichloroethylene under corresponding conditions were cited in other studies as about 10.7 months (Dilling et al. 1975) and 30 months (Pearson and McConnell 1975). It is not clear why there is such a large difference between these values; however, errors inherent in the extrapolation method used in the first approach (Jeffers et al. 1989) and the presence of transformation factors other than chemical hydrolysis, such as microbial degradation, in the second approach (Dilling et al. 1975; Pearson and McConnell 1975) may account for the discrepancy in the numbers.

An aerobic degradation study of trichloroethylene in seawater showed that 80% of trichloroethylene was degraded in 8 days (Jensen and Rosenberg 1975). Degradation products were not reported. Another study using domestic waste water as a microbial inoculum found that after the 1st week of incubation, 64 and 38% degradation was achieved for initial trichloroethylene concentrations of 5 and 10 ppm, respectively (Tabak et al. 1981). After the 4th week of incubation, these percentages were 87 and 84%, respectively. Microbial degradation products of trichloroethylene in groundwater were reported to be dichloroethylene and vinyl chloride (Smith and Dragun 1984).

Biotransformation was also strongly indicated as a factor in the degradation of trichloroethylene in a case of soil and groundwater pollution (Milde et al. 1988). The only ethylenes at the point source of pollution were tetrachloroethylene and trichloroethylene; however, substantial amounts of known metabolites of these two compounds (dichloroethylene, vinyl chloride, and ethylene) were found at points far from the source. Data from laboratory studies by the same group supported the study authors' contention that degradation was due to reductive dehalogenation by microorganisms. Microcosm studies of

trichloroethylene biotransformation in aquifers have also indicated that reductive dehalogenation is the primary degradation reaction (Dong et al. 2009; Parsons et al. 1985; Wilson et al. 1986). Squillace and Moran (2007) reported that concentrations of trichloroethylene in oxic groundwater sampled across the United States were approximately 2 orders of magnitude larger than in anoxic groundwater and cited a slower rate of biodegradation under oxic conditions. However, a field study of groundwater at the Lawrence Livermore National Laboratory found a highly oxidized environment in which no evidence of reductive dehalogenation of trichloroethylene was seen (McNab and Narasimhan 1994).

Since neither biodegradation nor hydrolysis occurs at a rapid rate, most trichloroethylene present in surface waters can be expected to volatilize into the atmosphere. However, because trichloroethylene is denser than and only moderately soluble in water, that which is not immediately volatilized may be expected to submerge and thus be removed from contact with the surface (Doust and Huang 1992).

6.3.2.3 Sediment and Soil

The majority of trichloroethylene present on soil surfaces will volatilize to the atmosphere or leach into the subsurface. Once trichloroethylene leaches into the soil, it appears not to become chemically transformed or undergo covalent bonding with soil components. When trichloroethylene was absorbed onto kaolinite and bentonite, the ^{13}C nuclear magnetic resonance (NMR) spectra showed no evidence of chemical reactions (Jurkiewicz and Maciel 1995). Because trichloroethylene is a dense nonaqueous phase liquid, it can move through the unsaturated zone into the saturated zone where it can displace soil pore water (Wershaw et al. 1994).

Biodegradation is favored only under limited conditions. When soil samples containing subsurface bacteria from depths of 1.2, 3.0, and 5.0 meters in a flood plain in Oklahoma were incubated with trichloroethylene for 16 weeks at 20°C, no detectable degradation of the chemical occurred (Wilson et al. 1983a). It has been shown that the biodegradation of trichloroethylene in soil increases with the organic content of the soil (Barrio-Lage et a. 1987). There is evidence that trichloroethylene may inhibit total soil biomass and fungi (Kanazawa and Filip 1986), possibly resulting in the inhibition of microbial transformation processes. However, the same authors observed an increase in anaerobic and specialized aerobic bacteria, which might indicate an opportunistic response to a suitable substrate by these microorganisms.

Degradation of trichloroethylene by anaerobes via reductive dehalogenation can yield vinyl chloride, a known carcinogen (Ensley 1991). In an anaerobic column operated under methanogenic conditions, 100% transformation of injected tetrachloroethylene and trichloroethylene to vinyl chloride was obtained after 10 days (Vogel and McCarty 1985). Addition of electron donors was demonstrated to promote further degradation to the more benign compound ethylene (Freedman and Gossett 1989).

Anaerobic incubations of trichloroethylene with soils collected from lotus, rice, and vegetable fields in Japan resulted in biodegradation rates that varied with soil type, temperature, and initial concentration of trichloroethylene (Yagi et al. 1992). The lotus field soils degraded >80% of the trichloroethylene after 42 days, while the degradation in vegetable field soils was minimal. A study by Walton and Anderson (1990) compared soil samples collected from a former chlorinated solvent disposal site and microbial degradation of trichloroethylene in vegetated (grass, a legume, a composite herb) and nonvegetated soils. Biomass determinations, disappearance of trichloroethylene from the headspace of spiked soil slurries, and mineralization of ^{14}C-trichloroethylene to radiolabelled carbon dioxide ($^{14}CO_2$) all showed that microbial activity is greater in vegetated soils and that trichloroethylene degradation occurs faster in the vegetated than in the nonvegetated soils. An anaerobic bacterium that dechlorinates tetrachloroethylene and trichloroethylene to ethylene using hydrogen as the electron donor has been isolated (Maymo-Gatell et al. 1997). The isolated strain did not appear to belong to any presently known genus or species.

Aerobic biodegradation of trichloroethylene occurs by cometabolism with aromatic compounds (Ensley 1991) and thus requires a cosubstrate such as phenol (Nelson et al. 1987, 1988) or toluene (Fan and Scow 1993). Trichloroethylene degradation by toluene-degrading bacteria has been demonstrated in the presence, but not absence, of toluene (Mu and Scow 1994). Isoprene, a structural analog of trichloroethylene, has also been used as a cosubstrate for trichloroethylene oxidation by some bacteria (Ewers et al. 1990). One source of inhibition of degradation in the absence of cosubstrate may be the toxicity of trichloroethylene itself to indigenous bacteria.

Bacteria have been found that use methane as an energy source and simultaneously degrade trichloroethylene using methane monooxygenase (Alvarez-Cohen and McCarty 1991a, 1991b; Bowman et al. 1993; Fox et al. 1990; Henry and Grbic-Galic 1991a, 1991b; Oldenhuis et al. 1991). Methane-utilizing bacteria were shown to aerobically degrade trichloroethylene to carbon dioxide in soil columns perfused with natural gas within 2 weeks (Wilson and Wilson 1985). Methanotrophs isolated from sediment likewise degraded 650 ng/mL of trichloroethylene in liquid culture to 200 ng/mL in 4 days (at 20°C), producing carbon dioxide and no dichloroethylene or vinyl chloride (Fogel et al. 1986). A

possible reason for the persistence of trichloroethylene in the environment despite these natural decomposition processes lies in the sensitive balance that must be maintained between enough cosubstrate to induce the degrading enzymes and too much cosubstrate, which could outcompete the trichloroethylene and inhibit its decomposition (Ensley 1991). Such balance may rarely be achieved in nature.

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

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

6.4.1 Air

Trichloroethylene is widely detected in ambient air. The U.S. EPA maintains the Air Quality System (AQS) database, which serves as a repository of criteria air pollutant and HAPs monitoring data from the United States, Puerto Rico, and the Virgin Islands. Tables 6-5 and 6-6 illustrate the annual mean percentile distributions of trichloroethylene from hundreds of monitoring sites for years 1998–2008 and 2010–2015, respectively. In general, most measured values for these years are <1 ppb; however, a measured value of 164 ppb was recorded in Lake County, Indiana on November 6, 2013 and a value of 49 ppb was recorded on May 3, 2011 in Klamath Falls, Oregon (EPA 2015a), which suggests that trichloroethylene levels are highly variable in the atmosphere depending upon whether or not there are significant point sources nearby.

The data presented in Tables 6-5 and 6-6 suggest a general decline in ambient air levels of trichloroethylene over the past 2 decades and are consistent with an analysis performed by McCarthy et al. (2007) of AQS data over three trend periods: 1990–2005, 1995–2005, and 2000–2005, which suggested a decrease of about 4–7% for the median trichloroethylene levels annually.

Table 6-5. Percentile Distribution of Annual Mean Trichloroethylene Concentrations (ppb) Measured in Ambient Air at Locations Across the United States[a]

Year	Number of U.S. locations	25th	50th	75th	95th	Maximum
1998	132	0.025	0.030	0.046	0.141	1.027
1999	170	0.025	0.030	0.050	0.158	0.815
2000	187	0.025	0.030	0.050	0.196	1.375
2001	205	0.021	0.025	0.039	0.097	2.399
2002	259	0.016	0.025	0.045	0.250	3.427
2003	250	0.025	0.030	0.050	0.250	1.287
2004	264	0.025	0.025	0.050	0.210	1.075
2005	328	0.025	0.027	0.048	0.179	1.234
2006	298	0.015	0.025	0.035	0.127	1.064
2007	317	0.016	0.025	0.030	0.091	0.750
2008	288	0.012	0.025	0.030	0.108	1.145

[a]Data originally reported in units parts per billion carbon but converted to ppb volume in the table.

Source: EPA 2011f

Table 6-6. Percentile Distribution of Annual Mean Trichloroethylene Concentrations (ppb) Measured in Ambient Air at Locations Across the United States[a]

Year	Number of U.S. locations	25th	50th	75th	95th	Maximum
2010	540	0.0028	0.021	0.13	0.16	1.24
2011	518	0.0017	0.019	0.12	0.15	3.14
2012	512	0.0018	0.015	0.12	0.15	1.08
2013	477	0.0015	0.015	0.12	0.15	3.19
2014	444	0.0011	0.015	0.12	0.14	0.52
2015	220	0.0000	0.0010	0.0033	0.018	0.24
2016	209	0.0000	0.0009	0.0055	0.023	0.1035
2017	178	0.0000	0.0000	0.0003	0.0099	0.0607
2018	159	0.0000	0.0000	0.0017	0.0128	0.0714

[a]Data originally reported in units parts per billion carbon but converted to ppb volume in the table.

Source: EPA 2018

Historical monitoring data for trichloroethylene in ambient air in the United States, prior to 1981, were compiled by EPA (1982d). This compilation, which includes over 2,300 monitoring points, reported mean trichloroethylene concentrations of 0.03 ppb in rural/remote areas, 0.460 ppb in urban/suburban areas, and 1.2 ppb in areas near emission sources of trichloroethylene. A similar compilation (EPA 1979a), which includes additional U.S. monitoring data and worldwide data, indicates that the ambient air mixing ratio of trichloroethylene is 0.01–0.03 ppb in the northern hemisphere and <0.003 ppb in the southern hemisphere. Slightly lower ambient air mixing ratios of 0.005–0.01 ppb have also been reported for the northern hemisphere (Class and Ballschmiter 1986; Fabian 1986).

Ambient air monitoring studies in the United States detected trichloroethylene concentrations of 0.24–3.9 μg/m^3 (0.04–0.72 ppb) in Portland, Oregon, in 1984 (Ligocki et al. 1985); 2.1 μg/m^3 (0.39 ppb) in Philadelphia, Pennsylvania, in 1983–1984 (Sullivan et al. 1985); 0.21–0.59 ppb in three New Jersey cities during the summer of 1981 and winter of 1982 (Harkov et al. 1984); and 0.096–0.225 ppb in seven cities (Houston, Texas; St. Louis, Missouri; Denver, Colorado; Riverside, California; Staten Island, New York; Pittsburgh, Pennsylvania; and Chicago, Illinois) in 1980–1981 (Singh et al. 1982). The mean and median concentrations of trichloroethylene in air samples collected at 25 sites across Minnesota between 1991 and 1998 were 0.43 and 0.21 μg/m^3 (0.08 and 0.04 ppb), respectively (Pratt et al. 2000); the reported lower detection limit was 0.04 μg/m^3. In the studies that discuss seasonal variation, levels were found to vary between the fall/winter season and the spring/summer season, with fall/winter levels usually higher. This is consistent with the observation that higher temperatures increase the rate of reaction with hydroxyl radicals and subsequent degradation of trichloroethylene (see Section 6.3.2.1).

The average trichloroethylene level detected in samples collected from ambient air in the Norwegian Arctic between 1982 and 1983 was 0.007 ppb (Hov et al. 1984). Average concentrations of trichloroethylene in Alaskan Arctic haze between 1980 and 1982 were 0.036 ppb in winter and 0.007 ppb in summer (Khalil and Rasmussen 1983).

Some elevated outdoor air levels of trichloroethylene are associated with waste disposal sites. Average trichloroethylene levels of 0.08–2.43 ppb were detected in ambient air at six landfill sites in New Jersey; the maximum concentration was 12.3 ppb (Harkov et al. 1985).

A survey of indoor air showed median concentrations of trichloroethylene as high as 27 μg/m^3 (5.0 ppb) in a North Carolina office building; 0.74 μg/m^3 (0.14 ppb) in a Washington, DC, school; and 0.82 μg/m^3 (0.15 ppb) in a Washington, DC, home for the elderly (Hartwell et al. 1985). The level of trichloro-

ethylene in the air of an indoor university laboratory was 0.008 ppm (8.0 ppb) (Nicoara et al. 1994). Gordon et al. (1999) detected trichloroethylene in the indoor air of two out of 185 homes in Arizona with a maximum concentration of 24 μg/m^3 (4.39 ppb); the detection limit was 1.8 μg/m^3 (0.33 ppb). Weisel et al. (2008) detected trichloroethylene in the air of 8 out of 100 homes located in both suburban and rural areas of New Jersey with maximum and 95th percentile values of 13 and 2.74 μg/m^3 (2.38 and 0.50 ppb), respectively; the detection limit was reported to be approximately 1 μg/m^3 (0.18 ppb). McKone (1987) estimated the levels of trichloroethylene in indoor air based on the properties of trichloroethylene and a three-compartment model. If the tap water contained 1 mg trichloroethylene/L (1,000 ppm), then the air in the shower during use was estimated to contain 0.018 mg/L (3.3 ppm), while the airborne trichloroethylene concentration in the rest of the house was estimated to be 0.11 mg/m^3 (0.02 ppm) during the day (7 am–11 pm) and 0.024 mg/m^3 (0.0044 ppm) during the night (11 pm–7 am).

Loh et al. (2006) measured geometric mean and maximum trichloroethylene concentrations of 0.43 and 115 μg/m^3 (0.08 and 21.1 ppb), respectively, in the air of over 100 stores in the greater Boston, Massachusetts area and 0.23 and 118 μg/m^3 (0.04 and 21.6 ppb), respectively, in the air of 20 dining establishments in the same region. Martin et al. (2005) measured the concentrations of trichloroethylene at buildings located near an industrial facility in Clark County, Georgia. The method limit of detection was 25 ng/m^3 (0.0046 ppb). Levels in indoor air were 0.92 μg/m^3 (0.17 ppb) at an elementary school, 0.59–1.85 μg/m^3 (0.11–0.34 ppb) at a local business, and 0.21–4.66 μg/m^3 (0.04–0.85 ppb) in three homes. Levels measured in outdoor air at these same locations were 0.72 μg/m^3 (0.13 ppb), 1.30–4.59 μg/m^3 (0.24–0.84 ppb), and 0.03–0.05 μg/m^3 (0.005–0.009 ppb), respectively.

Mean concentrations of trichloroethylene measured during the Minnesota Children's Pesticide Exposure Study (MCPES) were 0.8 μg/m^3 (0.15 ppb) in 73 personal air samples, 0.6 μg/m^3 (0.11 ppb) in 101 indoor air samples, and 0.6 μg/m^3 (0.11 ppb) in 100 outdoor air samples collected from households with children; the mean detection limit was 0.2 μg/m^3 (0.037 ppb) (Adgate et al. 2004a). During the School Health Initiative: Environment, Learning, Disease (SHIELD) study, the concentrations of trichloroethylene were measured in the outdoor home air, indoor school air, indoor home air, and personal air of 113 children from two inner-city schools in Minneapolis, Minnesota (Adgate et al. 2004b). Median concentrations of trichloroethylene in each of these sampling groups during both summer and winter were between 0.1 and 0.3 μg/m^3 (0.02–0.05 ppb); between 56 and 90% of the samples were above an unspecified detection limit. The mean concentrations of trichloroethylene measured in the winter during the Toxic Exposure Assessment, Columbia/Harvard (TEACH) study were 0.36 μg/m^3 (0.07 ppb) in home outdoor air, 1.26 μg/m^3 (0.23 ppb) in home indoor air, and 2.62 μg/m^3 (0.48 ppb) in personal air

associated with 36 students from west central Harlem in New York City (Kinney et al. 2002). Trichloroethylene concentrations measured in the summer were 0.24 μg/m^3 (0.04 ppb) in home outdoor air, 0.32 μg/m^3 (0.06 ppb) in home indoor air, and 0.51 μg/m^3 (0.09 ppb) in personal air associated with 31–40 students from the same area. The limit of detection was 0.15 μg/m^3 (0.027 ppb). Clayton et al. (1999) reported mean trichloroethylene levels of 5.27 μg/m^3 (0.96 ppb) in 386 personal air samples, 39.4% of which were above an unspecified limit of detection, 2.84 μg/m^3 (0.52 ppb) in 402 indoor air samples (36.1% above the limit of detection), and 1.11 μg/m^3 (0.20 ppb) in 97 outdoor air samples (26.4% above the limit of detection) collected in EPA Region 5.

Brenner (2010) measured median and maximum trichloroethylene concentrations of 0.895 and 1.69 μg/m^3 (0.16 and 0.31 ppb), respectively, for 541 indoor air samples from four large buildings at the NASA Ames Research Center at the southern end of San Francisco Bay; the frequency of detection was 99.8%. The levels were attributed to vapor intrusion from underlying contaminated groundwater. Vapor intrusion is the process whereby trichloroethylene may evaporate from contaminated groundwater and soil and migrate into air spaces beneath buildings to enter the indoor air (EPA 2002). Burk and Zarus (2013) reported selected results from 135 vapor intrusion public health assessments and consultations for 121 sites published on ATSDR's website between 1994 and 2009. Trichloroethylene indoor air levels were attributed to vapor intrusion and detected at 21 sites; levels at 3 of these sites were high enough to be considered a public health hazard.

Sapkota et al. (2005) reported median and maximum trichloroethylene concentrations of 3.11 and 6.89 μg/m^3 (0.57 and 1.26 ppb), respectively, in the indoor air of a tollbooth at the Baltimore Harbor Toll Plaza and 0.06 and 0.56 μg/m^3 (0.01 and 0.10 ppb), respectively, in the air outside the tollbooth.

6.4.2 Water

The concentration of trichloroethylene in the open oceans may be an indication of the environmental background levels in water. Levels in open waters of the Gulf of Mexico were below the detection level of 1 part per trillion (ppt) (Sauer 1981). Average levels of 7 ng/L (7 ppt), 0.3 ppt, and 74 ng/L (74 ppt) were found in the northeastern Atlantic (Murray and Riley 1973), Liverpool Bay (Pearson and McConnell 1975), and the southern North Sea (Huybrechts et al. 2005), respectively.

Trichloroethylene has been detected in many samples taken from drinking water supplied by contaminated sources from which trichloroethylene and other volatile organic compounds are not always

completely removed by conventional water treatment. The EPA (2011d) released the results of its second 6-year review of 69 regulated contaminants in public water systems (PWS) located across the United States. Data for trichloroethylene are summarized in Table 6-7. During 2005, trichloroethylene was detected in 2,292 out of 46,937 samples (4.9%) collected from groundwater supplied PWS and 1,874 out of 12,705 samples (14.8%) collected from surface water supplied PWS. The median, 95th percentile, and maximum concentrations of the positive samples were 1.1, 13.0, and 159 ppb, respectively, in groundwater supplied PWS and 1.6, 28.0, and 50.0 ppb, respectively, in the surface water supplied PWS. Rowe et al. (2007) detected trichloroethylene in 41 out of 1,207 U.S. domestic well samples collected between 1996 and 2002, a detection frequency of 3.4%. The EPA Groundwater Supply Survey of finished water from 945 drinking water systems nationwide using groundwater sources found trichloroethylene in 91 water systems (detection limit 0.2 ppb); the median level of the positive samples was approximately 1 μg/L (ppb), with a single maximum level of 130 μg/L (ppb) (Westrick et al. 1984).

Williams et al. (2002) reported annual levels of trichloroethylene measured in 3,447–4,226 California drinking water sources between 1995 and 2001. Trichloroethylene was detected in 9.6–11.7% of the sources over the time period with an average detected concentration ranging from 14.2 to 20.7 μg/L (ppb). Trichloroethylene was detected in groundwater samples from approximately 55% of 30 public supply wells and 10% of 95 monitoring wells located in a region of southern New Jersey (Stackelberg et al. 2001). The maximum concentrations of trichloroethylene measured in community water systems near Dayton, Ohio during 2004 were 3.29 μg/L (ppb) in source water and 0.21 μg/L (ppb) in finished water (Rowe et al. 2007). Trichloroethylene levels ranging from 10 to 250 ng/L (0.01–0.25 ppb) were found in tap water from homes in the vicinity of the Love Canal waste site in New York (Barkley et al. 1980).

Drinking water supplies at Camp Lejeune have been shown to be heavily contaminated with trichloroethylene and other chlorinated solvents due to handling and disposal practices of an off-site dry cleaning facility (ATSDR 2017b). Water samples obtained from the Hadnot Point Water Treatment plant at Camp Lejeune had levels of trichloroethylene of up to 1,400 μg/L in 1982 (ATSDR 2017b). A recent historical reconstruction study of this site, which applied additional modeling methods, reported trichloroethylene concentrations at the Hadnot Point water treatment plant reached a maximum monthly average value of 783 μg/L compared to a one-time maximum measured value of 1,400 μg/L during the period of August 1953 to December 1984 (Maslia et al. 2016).

Table 6-7. Concentrations of Trichloroethylene (ppb) Measured in Drinking Water from Public Water Systems (PWS) Across the United States

	Year	Total samples	Positive detections[a]	Mean[b]	Median[b]	95th Percentile[b]	Maximum
Groundwater supplied PWS							
	1998	29,356	1,308 (4.5%)	2.99	1.20	11.0	39.3
	1999	29,695	1,383 (4.6%)	3.05	1.30	11.8	47.0
	2000	32,794	1,545 (4.7%)	2.76	1.20	9.00	49.0
	2001	36,657	1,713 (4.7%)	3.55	1.30	13.0	71.6
	2002	43,934	2,119 (4.8%)	3.72	1.40	13.0	58.7
	2003	42,466	2,199 (5.2%)	3.67	1.60	13.8	58.0
	2004	46,490	2,283 (4.9%)	3.70	1.30	15.0	90.9
	2005	46,937	2,292 (4.9%)	3.33	1.10	13.0	159
Surface water supplied PWS							
	1998	9,020	1,628 (18%)	5.69	2.50	29.0	50.0
	1999	11,415	1,877 (16%)	6.09	2.50	25.3	50.0
	2000	11,521	1,696 (15%)	5.70	2.00	28.3	50.0
	2001	11,913	2,085 (18%)	4.71	1.46	19.9	50.0
	2002	13,287	1,926 (14%)	4.86	1.60	20.1	50.0
	2003	12,605	1,813 (14%)	4.43	1.50	19.4	50.0
	2004	12,814	1,816 (14%)	4.80	1.80	22.0	50.0
	2005	12,705	1,874 (15%)	5.40	1.60	28.0	50.0

[a]Limit of detection for most samples was 0.5 ppb.
[b]Mean, median, and 95th percentile concentrations of positive detections.

Source: EPA 2011d

A summary of U.S. groundwater analyses from both federal and state studies reported that trichloroethylene was the most frequently detected organic solvent and the one present in the highest concentration (Dyksen and Hess 1982). Trichloroethylene was detected in 388 of 669 groundwater samples collected in New Jersey from 1977 to 1979, with a maximum concentration of 635 ppb (Page 1981). Maximum concentrations ranging from 900 to 27,300 ppb trichloroethylene were found in contaminated wells from four states (Pennsylvania, New York, Massachusetts, and New Jersey) (Burmaster 1982).

A possible source for much of the groundwater contamination is landfill leachate containing trichloroethylene. Trichloroethylene was the most commonly found chemical at NPL sites in New York State (Mumtaz et al. 1994). The compound was detected in leachate samples from 5 of 6 Minnesota municipal solid waste landfills at levels ranging from 0.7 to 125 μg/L (ppb) and in groundwater near 9 of 13 landfills at levels ranging from 0.2 to 144 μg/L (ppb) (Sabel and Clark 1984). Trichloroethylene was also detected in landfill leachate from a landfill in New Jersey at concentrations of up to 7,700 μg/L (ppb) (Kosson et al. 1985). Trichloroethylene has also been detected in ground water at the U.S. Army Cold Regions Research and Engineering Laboratory in Hanover, New Hampshire, where it was used as a refrigerant between 1960 and 1987 (Hewitt and Shoop 1994). In water collected directly after well instillation, the trichloroethylene concentrations were 0.0059–160 mg/L (ppm); detection limits were <0.0005 mg/L (ppm). Average trichloroethylene concentrations measured in groundwater at different locations at a Superfund site (former auto parts manufacturing) located on the shore of Lake Michigan ranged from 14.6 to 6,554 μg/L (ppb) (An et al. 2004). The average concentration measured in sediment water collected 100 m offshore from the site was 1.37 μg/L (ppb); the reported detection limit for chlorinated ethenes was 0.5 μg/L (ppb). Brusseau et al. (2007) reported concentrations of trichloroethylene ranging from 100 to approximately 12,000 μg/L (ppb) in groundwater collected at the Tucson International Airport Area federal Superfund site in Southern Arizona.

An analysis of the EPA STORET Data Base (1980–1982) found that trichloroethylene had been positively detected in 28% of 9,295 surface water reporting stations nationwide (Staples et al. 1985). Data from January through December of 2015 indicated that trichloroethylene was detected in 5 out of 298 river/stream samples in the United States at levels ranging from 0.20 to 8.6 μg/L (ppb) (EPA 2015c). An analysis of 1,350 samples taken from 1978 to 1979 and 4,972 samples from 1980 to 1981 from the Ohio River system found a similar percentage of positive detections; most positive samples had trichloroethylene levels of 0.1–1.0 ppb (Ohio River Valley Sanitation Commission 1980, 1982). Trichloroethylene was detected in 261 of 462 surface water samples collected in New Jersey from 1977 to

1979, with a maximum concentration of 32.6 ppb (Page 1981). Mean trichloroethylene levels of 0.008 and 0.13 µg/L (ppb) were reported for water samples collected from the lower Niagara River and Lake Ontario in 1981 (Strachan and Edwards 1984); trichloroethylene was detected in 12/17 samples from the Niagara River and 16/83 samples from Lake Ontario. Asher et al. (2007) measured trichloroethylene concentrations ranging from 0.15 to 0.32 µg/L (ppb) in a section of the Aberjona River near Woburn, Massachusetts; the limit of detection was 0.02 µg/L (ppb).

Rain water collected in Portland, Oregon, in 1984 contained trichloroethylene levels of 0.78–16 ng/L (0.78–16 ppt) (Ligocki et al. 1985). An average trichloroethylene concentration of 5 ng/L (5 ppt) was found in rain water from La Jolla, California, and levels of 30 and 39 ppt were identified in snow from southern California and Alaska, respectively (Su and Goldberg 1976). Levels up to 150 ng/L (150 ppt) were found in samples collected in rainwater in industrial cities in England (Pearson and McConnell 1975). Rainwater samples collected in Tokyo between October 1989 and September 1990 had a mean trichloroethylene level of 136 ng/L (136 ppt), with higher levels in samples obtained during the winter (Jung et al. 1992).

Monitoring wells at 30 sites in Salt Lake Valley, Utah were used to analyze VOCs including trichloroethylene). Trichloroethylene was detected in five of the wells at maximum concentration of 1.54 µg/L (ppb) and a minimum concentration of 0.02 µg/L (ppb). These values were both under the maximum contaminant level of 5 µg/L (ppb) (USGS 2003).

Samples from 2,401 domestic and 1,096 public wells across the nation were monitored for VOCs. Approximately 3,500 water samples were collected during 1985–2001. Concentrations of human-health concern (defined in the report as concentrations greater than an EPA MCL or concentrations greater than the health-based screening level) for trichloroethylene were found in both domestic and public wells. Trichloroethylene was the 4th most frequently detected VOC in the study and had the highest median concentration of all VOC detections. At an assessment level of 0.2 µg/L (ppb), the overall detection frequency for trichloroethylene was about 3% and was higher in the public well samples than in the domestic samples, approximately 4 and 1%, respectively. At an assessment level of 0.02 µg/L (ppb), the detection frequency was close to 4%. It was noted that concentrations with potential concern could not be directly related to concentrations in drinking water that would cause concern due to the nature of the sampling. (USGS 2006).

6.4.3 Sediment and Soil

A maximum trichloroethylene level of 9.9 ppb was found in sediment from Liverpool Bay, England (Pearson and McConnell 1975). Sediment levels from nondetectable to 0.2 ppb (wet weight) trichloroethylene were found in Lake Pontchartrain near New Orleans (Ferrario et al. 1985). An analysis of the EPA STORET Data Base (1980–1982) found that trichloroethylene had been positively detected in sediment samples taken at 6% of 338 observation stations, with median levels of <5 μg/kg (dry weight) (<5 ppb) (Staples et al. 1985). The observation stations included both "ambient" and "pipe" sites. Ambient sites include streams, lakes, and ponds and are intended to be indicative of general U.S. waterway conditions. Pipe sites refer to municipal or industrial influents or effluents.

Trichloroethylene was qualitatively detected in the soil/sediment matrix of the Love Canal waste site near Niagara Falls (Hauser and Bromberg 1982). Sediment concentrations were found to be <0.5 μg/kg (dry weight) (<0.5 ppb) near a discharge point for effluent containing 17 ppb trichloroethylene in Los Angeles (Gossett et al. 1983).

Trichloroethylene in soil and groundwater were found to be correlated (r^2 0.9994) in samples taken during well instillation at the U.S. Army Cold Regions Research and Engineering Laboratory in Hanover, New Hampshire (Hewitt and Shoop 1994). Concentrations of trichloroethylene in soil from the saturated zone were 0.008–25 mg/kg (ppb), while concentrations in the groundwater were 44–180,000 ppb.

Soil gas, at three former fuel-dispensing sites in Fort Gorgon, Georgia, was monitored from October 2010 to September 2011 (USGS 2012). Fifty-five soil-gas samplers were installed at one site, 30 samplers at another site, and 39 samplers at the third site. The method detection limit was 0.02 μg/L (ppb). Trichloroethylene was not detected in the majority of the samples; however, it was detected just below the detection limit in two of the samples and detected at a mass of 0.05 μg in one of the samples (USGS 2012).

6.4.4 Other Environmental Media

Trichloroethylene was detected in 30 table-ready food items collected from supermarkets across the United States during a 5-year study (1996–2000) conducted by the U.S. Food and Drug Administration (Fleming-Jones and Smith 2003). Minimum and maximum concentrations are listed in Table 6-8. Reported concentrations were between 2 and 10 ppb in most items. However, maximum levels were much higher in beef frankfurters (105 ppb), chocolate cake with icing (57 ppb), raw avocado (75 ppb),

Table 6-8. Levels of Trichloroethylene Measured in Table-Ready Foods from Across the United States During a 5-Year Study (1996–2000)

Type of food	Positive detections	Minimum (ppb)	Maximum (ppb)
American cheese	2	2	2
Cheddar cheese	1	2	2
Mixed nuts	2	2	5
Ground beef	2	3	6
Banana raw	1	2	2
Cream cheese	2	2	3
Frankfurters, beef	5	2	105
Chocolate cake with icing	3	3	57
Tuna, canned in oil	2	9	11
Fruit-flavored cereal	1	3	3
Peanut butter	3	4	70
Avocado, raw	6	2	75
Popcorn, popped in oil	2	4	8
Blueberry muffin	2	3	4
Orange, raw	1	2	2
Coleslaw with dressing	1	3	3
Sweet roll/danish	3	3	4
Potato chips	4	4	140
Quarter pound hamburger, cooked	2	5	9
Margarine	3	2	21
Butter	2	7	9
Chocolate chip cookies	2	2	4
Apple pie, fresh/frozen	2	2	4
Chicken nuggets, fast food	3	2	5
French fries, fast food	2	3	3
Cheeseburger, quarter pound	1	7	7
Cheese pizza	1	2	2
Bologna	5	2	20
Cheese and pepperoni pizza	2	2	2
Cake doughnuts with icing	1	3	3

Source: Fleming-Jones and Smith 2003

and potato chips (140 ppb). McConnell et al. (1975) reported the detection of trichloroethylene in dairy products (milk, cheese, butter) at 0.3–10 μg/kg (ppb), meat (English beef) at 12–16 ppb, oils and fats at 0–19 ppb, beverages (canned fruit drink, light ale, instant coffee, tea, wine) at 0.02–60 ppb, fruits and vegetables (potatoes, apples, pears, tomatoes) at 0–5 ppb, and fresh bread at 7 ppb. Samples obtained from a food processor in Pennsylvania contained trichloroethylene concentrations of 68 ppb in plant tap water, 28 ppb in Chinese-style sauce, 40 ppb in quince jelly, 25 ppb in crab apple jelly, 20 ppb in grape jelly, and 50 ppb in chocolate sauce (Entz and Hollifield 1982). Various samples of U.S. margarine were found to contain trichloroethylene levels of 440–3,600 ng/g (ppb) (Entz et al. 1982). An analysis of intermediate grain-based foods in 1985 found the following trichloroethylene levels (in ppb concentrations): corn muffin mix (0.0); yellow corn meal (2.7); fudge brownie mix (2.4); dried lima beans (0.0); lasagna noodles (0.0); bleached flour (0.77); uncooked rice (0.0); and yellow cake mix (1.3) (Heikes and Hopper 1986).

Another study found that trichloroethylene can be absorbed from the atmosphere by foods and concentrated over time, so that acceptable ambient air levels may still result in food levels that exceed acceptable limits (Grob et al. 1990). The authors estimated that in order to limit food concentrations of trichloroethylene to 50 μg/kg (ppb; the maximum tolerated limit for food halocarbons in Switzerland), the level in surrounding air should not exceed 38.5 $\mu g/m^3$ (7 ppb). Since the accepted levels found near emission sources are often far above this limit, foods processed or sold near these sources may routinely exceed the tolerated trichloroethylene concentration, thus making the setting of air emission standards problematic. It is also noteworthy that the limits recommended by Grob et al. (1990) exceed acceptable ambient air concentrations for many regions of the United States (see Chapter 8).

An analysis of six municipal solid waste samples from Hamburg, Germany, revealed levels of trichloroethylene ranging from undetectable to 0.59 mg/kg (ppm) (Deipser and Stegmann 1994). In a study analyzing automobile exhaust for chlorinated compounds, trichloroethylene was not detected (Hasanen et al. 1979).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The most important routes of exposure to trichloroethylene for most members of the general population appear to be inhalation of the compound in ambient air and ingestion of drinking water. Available data indicate that dermal exposure is not an important route for most people. General population exposure from inhalation of ambient air varies widely depending on location. In general, rural areas exhibit lower

background concentrations of trichloroethylene as compared to urban areas. One study comparing differences in trichloroethylene levels reported a significant difference in values between rural and urban workers with average blood trichloroethylene levels of 0.180 and 0.763 ng/L (763 ppb), respectively (Brugnone et al. 1994). A study of an urban population was conducted using the residents of the city of Zagreb, Croatia (Skender et al. 1994). Blood concentration levels of trichloroethylene and tetrachloroethylene among the residents ranged from <0.015 to 0.090 μg/L (ppb). The concentrations in drinking water in the city were <0.05–22.93 and 0.21–7.80 μg/L (ppb) for trichloroethylene and tetrachloroethylene, respectively.

The Fourth National Report on Human Exposure to Environmental Chemicals (CDC 2018) includes results from assessment of trichloroethylene levels in blood samples from 923 cigarette smokers and 2,054 nonsmokers within the U.S. general population surveyed during the years 2013 and 2014 (Table 6-9). Trichloroethylene was below the detection limit of 0.012 ng/mL (ppb).

Assuming a typical air concentration range of 100–500 ppt (Singh et al. 1981, 1982) and a breathing rate of 20 m^3 air/day, the average daily air intake of trichloroethylene can be estimated at 11–33 μg/day. Average daily water intake of trichloroethylene can be estimated at 2–20 μg/day, assuming a typical concentration range of 2–7 ppb and consumption of 2 L water/day.

Because of the high propensity of trichloroethylene to volatilize from water, inhalation may be a major route of exposure in homes supplied with contaminated water (Andelman 1985b). In two homes (using well water containing the relatively high level of 40,000 ppb trichloroethylene), a running shower was found to elevate trichloroethylene levels in bathroom air from <0.5 to 81 mg/m^3 (93–15,072 ppb) in <30 minutes (Andelman 1985a). Significantly elevated indoor air levels of trichloroethylene (as compared to normal outdoor levels) have been found in various buildings, but the elevated levels seem to be related to new building construction using products containing trichloroethylene solvents or consumer products containing trichloroethylene (Hartwell et al. 1985; Wallace et al. 1987).

Trichloroethylene levels monitored in expired breath of 190 New Jersey residents were correlated with personal exposure levels, which were consistently higher than outdoor air levels and were instead attributed to indoor air levels (Wallace et al. 1985). Other studies have expanded upon and confirmed these findings, concluding that indoor air is a more significant exposure source of trichloroethylene than

Table 6-9. Geometric Mean and Selected Percentiles of Blood Concentrations (in ng/mL) for the U.S. Population from the National Health and Nutrition Examination Survey

	Survey years[a]	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Total	01–02	*[b]	<LOD[c]	<LOD	<LOD	<LOD	922
	03–04	*	<LOD	<LOD	<LOD	<LOD	1,228
	05–06	*	<LOD	<LOD	<LOD	<LOD	3,178
	07–08	*	<LOD	<LOD	<LOD	<LOD	2,952
	09–10	*	<LOD	<LOD	<LOD	<LOD	3,342
	11–12	*	<LOD	<LOD	<LOD	<LOD	2,694
	13–14	*	<LOD	<LOD	<LOD	<LOD	3,103
Age group							
12–19 years	05–06	*	<LOD	<LOD	<LOD	<LOD	937
	07–08	*	<LOD	<LOD	<LOD	<LOD	473
	09–10	*	<LOD	<LOD	<LOD	<LOD	568
	11–12	*	<LOD	<LOD	<LOD	<LOD	496
	13–14	*	<LOD	<LOD	<LOD	<LOD	581
20–59 years	01–02	*	<LOD	<LOD	<LOD	<LOD	922
	03–04	*	<LOD	<LOD	<LOD	<LOD	1,228
	05–06	*	<LOD	<LOD	<LOD	<LOD	1,562
	07–08	*	<LOD	<LOD	<LOD	<LOD	1,592
	09–10	*	<LOD	<LOD	<LOD	<LOD	1,840
≥20 years	11–12	*	<LOD	<LOD	<LOD	<LOD	2,198
	13–14	*	<LOD	<LOD	<LOD	<LOD	2,522
≥60 years	05–06	*	<LOD	<LOD	<LOD	<LOD	679
	07–08	*	<LOD	<LOD	<LOD	<LOD	887
	09–10	*	<LOD	<LOD	<LOD	<LOD	934
Gender							
Males	01–02	*	<LOD	<LOD	<LOD	<LOD	434
	03–04	*	<LOD	<LOD	<LOD	<LOD	604
	05–06	*	<LOD	<LOD	<LOD	<LOD	1,504
	07–08	*	<LOD	<LOD	<LOD	<LOD	1,466
	09–10	*	<LOD	<LOD	<LOD	<LOD	1,647
	11–12	*	<LOD	<LOD	<LOD	<LOD	1,343
	13–14	*	<LOD	<LOD	<LOD	<LOD	1,492
Females	01–02	*	<LOD	<LOD	<LOD	<LOD	488
	03–04	*	<LOD	<LOD	<LOD	<LOD	624
	05–06	*	<LOD	<LOD	<LOD	<LOD	1,674
	07–08	*	<LOD	<LOD	<LOD	<LOD	1,486
	09–10	*	<LOD	<LOD	<LOD	<LOD	1,695
	11–12	*	<LOD	<LOD	<LOD	<LOD	1,351
	13–14	*	<LOD	<LOD	<LOD	<LOD	1,611
Race/ethnicity							
Mexican Americans	01–02	*	<LOD	<LOD	<LOD	<LOD	228
	03–04	*	<LOD	<LOD	<LOD	<LOD	224
	05–06	*	<LOD	<LOD	<LOD	<LOD	773
	07–08	*	<LOD	<LOD	<LOD	<LOD	572
	09–10	*	<LOD	<LOD	<LOD	<LOD	666
	11–12	*	<LOD	<LOD	<LOD	<LOD	284
	13–14	*	<LOD	<LOD	<LOD	<LOD	495

Table 6-9. Geometric Mean and Selected Percentiles of Blood Concentrations (in ng/mL) for the U.S. Population from the National Health and Nutrition Examination Survey

	Survey years[a]	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Non-Hispanic blacks	01–02	*	<LOD	<LOD	<LOD	<LOD	191
	03–04	*	<LOD	<LOD	<LOD	<LOD	266
	05–06	*	<LOD	<LOD	<LOD	<LOD	828
	07–08	*	<LOD	<LOD	<LOD	<LOD	583
	09–10	*	<LOD	<LOD	<LOD	<LOD	598
	11–12	*	<LOD	<LOD	<LOD	<LOD	724
	13–14	*	<LOD	<LOD	<LOD	<LOD	600
Non-Hispanic whites	01–02	*	<LOD	<LOD	<LOD	<LOD	441
	03–04	*	<LOD	<LOD	<LOD	<LOD	644
	05–06	*	<LOD	<LOD	<LOD	<LOD	1,341
	07–08	*	<LOD	<LOD	<LOD	<LOD	1,329
	09–10	*	<LOD	<LOD	<LOD	<LOD	1,520
	11–12	*	<LOD	<LOD	<LOD	<LOD	927
	13–14	*	<LOD	<LOD	<LOD	<LOD	1,256
All Hispanics	11–12	*	<LOD	<LOD	<LOD	<LOD	572
	13–14	*	<LOD	<LOD	<LOD	<LOD	795
Asians	11–12	*	<LOD	<LOD	<LOD	<LOD	389
	13–14	*	<LOD	<LOD	<LOD	<LOD	344

[a]Survey period 2001–2002 is a one-third subsample of 20–59-year-olds; survey period 2003–2004 is a one-half subsample of 20–59-year-olds.
[b]Not calculated; the proportion of results below the LOD was too high to provide a valid result.
[c]<LOD means less than the limit of detection of 0.012 ng/mL (ppb).

CI = confidence interval; LOD = limit of detection

Source: CDC 2018

outdoor air, even near major point sources such as chemical plants (Adgate et al. 2004a, 2004b; Clayton et al. 1999; Kinney et al. 2002; Wallace 1986; Wallace et al. 1986a, 1986b, 1986c, 1986d). Wallace et al. (1989) reported air concentrations for four homes (nine samples per home) in North Carolina and found that indoor air concentrations of trichloroethylene in all homes were consistently higher than the outdoor concentrations. In fact, trichloroethylene did not have a measurable median outdoor air concentration, while median indoor values ranged from 0.95 to 26 μg/m^3 (0.2–4.8 ppb).

Correlations of exposure with other measures of body burden are often difficult and their results are consequently less conclusive. For example, trichloroethylene was present at unspecified levels in eight of eight samples of mother's milk from four urban areas in the United States (Pellizzari et al. 1982). Whole-blood specimens from 121 men and 129 women with no known exposure to trichloroethylene had levels from nondetectable to 1.5 ppb (Antoine et al. 1986). Postmortem analyses of human tissue revealed body fat levels of 1.4–32 μg/kg (ppb) (wet weight) among males and females with unspecified exposures (McConnell et al. 1975).

Various consumer products have been found to contain trichloroethylene. These include wood stains, varnishes, and finishes; lubricants; adhesives; typewriter correction fluids; paint removers; and cleaners (EPA 1987j). Trichloroethylene use as an inhalation anesthetic, fumigant, and extractant for decaffeinating coffee has been discontinued in the United States (EPA 1985c).

Contamination of drinking water supplies with trichloroethylene varies with location and with the drinking water source (surface water or groundwater). Generally higher levels are expected in groundwater because trichloroethylene volatilizes rapidly from surface water. There is some evidence that trichloroethylene can be produced in small amounts during the chlorination process of waste water treatment (Bellar et al. 1974), although no evidence exists for its formation through drinking water chlorination (Westrick et al. 1984).

Exposure to trichloroethylene via drinking water and the effects of pregnancy outcomes has been evaluated in residents of base family housing at Camp Lejeune in Onslow County, North Carolina (ATSDR 1998). In 1982, two drinking water supplies that were monitored over a 34-month period at Camp Lejeune were found to be contaminated with VOCs including trichloroethylene. Close monitoring was conducted as a means for the restoration program, and contamination has not been detected in these systems since February of 1985. The highest level of trichloroethylene measured in tap water samples was 1,400 ppb. The primary source of the contamination was attributed to a dry cleaning establishment.

There were 141 short-term exposed women, 31 long-term exposed women, and 5,681 unexposed women studied with regard pregnancy and mean birth weight (MBW), small for gestational age (SGA) and preterm birth. Results found that preterm delivery was not associated with exposure. A difference between the MBW of the long-term exposed women and the unexposed women was -139 g (90% confidence limit). The OR was 1.5 for SGA (90% confidence limit) and long-term exposure. For male births, the OR for SGA was 3.9 (90% confidence limit) and the difference in MBW for this group was -312 (90% confidence limit). Short-term exposed women had a lower occurrence of SGA infants and the MBW was slightly higher than infants of unexposed women. Further investigation with a larger group of participants was suggested to examine the potentially important link between reduced birth weight and SGA in male infants born to mothers who have been exposed, long-term, to trichloroethylene.

The National Occupational Exposure Survey (NOES), conducted by NIOSH from 1981 to 1983, estimated that 401,000 workers employed at 23,225 plant sites were potentially exposed to trichloroethylene in the United States (NIOSH 1990). The NOES database does not contain information on the frequency, concentration, or duration of exposures; the survey provides only estimates of workers potentially exposed to chemicals in the workplace.

The majority of data regarding worker exposure to trichloroethylene were obtained from degreasing operations, which is the primary industrial use of trichloroethylene (Bakke et al. 2007; Franco et al. 2007; Green et al. 2004; Murata et al. 2010; Raaschou-Nielson et al. 2001; Rosa 2003; von Grote et al. 2003). Worker exposure data indicated that exposure is likely to vary, although TWA concentrations were generally consistent and usually ranged from ≤50 to 100 ppm (NCI 1985). More recent occupational monitoring data from the United States were not located. von Grote et al. (2003) reviewed historical occupational exposure measurements at facilities in Europe and reported average workplace air concentrations measured between 1980 and 2000 generally between <1.0 and 15.4 ppm with 95th percentile values of <170 ppm. OSHA allows an 8-hour TWA permissible exposure limit of 100 ppm (Rosa 2003). The 15-minute TWA exposure, which should not be exceeded at any time during a workday, is 300 ppm (OSHA 1993; Rosa 2003). Higher-than-normal workplace exposure was generally attributable to poor workplace practices (improper operating procedures, negligence with regard to equipment maintenance or repair) and/or inadequate engineering controls. TWA concentrations from personal monitoring ranged from 1.2 to 5.1 ppm at individual industrial sites where trichloroethylene was used during the process of filling spray cans with insecticide and where trichloroethylene was used as a solvent during the formation of fiberglass aircraft components (NCI 1985). Workers at a clock manufacturing facility located in Bangkok, Thailand where trichloroethylene was used as a degreasing

agent had much higher urinary trichloroacetic acid (TCA) levels when compared to a control group (Singthong et al. 2015). Analysis of the air in the breathing zone of the manufacturing facility showed an average trichloroethylene level of 27.83±6.02 ppm. Average TCA levels in exposed workers and a nonoccupationally exposed control group of subjects was 14.84±1.62 and 2.95±0.28 mg/L, respectively.

Worker exposure in the dry cleaning industry is a notable route for exposure to trichloroethylene. Exposure was evaluated using the relationship between concentrations of trichloroethylene in urine and concentrations in air collected at the breathing zone of workers in the workplace. Forty participants between the ages of 27 and 57 included 30 dry cleaning workers and 10 occupationally non-exposed individuals as a reference. The mean values for exposure of trichloroethylene in the breathing zone were found to be 1.56, 1.75, and 2.40 mg/m^3 (0.20, 0.32, and 0.44 ppm) for sites with a dry cleaning machine capacities of 8, 12, and 18 kg, respectively. The mean value for exposure of trichloroethylene in the breathing zone for the occupationally non-exposed participants was 0.98 mg/m^3 (0.18 ppm). Mean urinary concentrations before and after work shifts were measured. Levels before work were 2.38, 5.53, and 8.18 µg/L (ppb) and levels after work were 4.46, 11.31, and 4.46 µg/L (ppb) at sites with the dry cleaning machine capacity of 8, 12, and 18 kg, respectively. For occupationally non-exposed participants, levels were 0.31 µg/L (ppb) before work and 0.29 µg/L (ppb) after work (Rastkari et al. 2011).

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 than adults. 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 may spend more time outdoors. Children also are generally closer to the ground and have not yet developed the adult capacity to judge and take actions to avoid hazards (NRC 1993).

As with adults, children are expected to be exposed to trichloroethylene through inhalation of ambient air and ingestion of drinking water. Children may also be exposed to trichloroethylene through ingestion of food containing this substance. The potential for exposure to trichloroethylene through ingestion of dust and soil is expected to be low based on the low to moderate potential for soil adsorption and the high rate of volatilization. Trichloroethylene has been detected in breast milk, indicating that this is a potential source of exposure for infants (Pellizzari et al. 1982). Beamer et al. (2012) detected trichloroethylene in 7 of 20 (35%) breast milk samples at a maximum concentration of 6 ng/mL. It was noted that the concentration in the breast milk was correlated to the concentration of trichloroethylene in water used for bathing and laundry (Beamer et al. 2012).

During the School Health Initiative: Environment, Learning, Disease (SHIELD) study, trichloroethylene was detected in only 3–7% of 416 blood samples collected from U.S. children from two neighborhoods in Minneapolis, Minnesota between 2000 and 2001 (Sexton et al. 2005). The 99th percentile concentration was reported as 0.01–0.02 ng/mL (ppb). Trichloroethylene was detected in <10% of blood samples collected from 43 children from a third Minneapolis neighborhood between 2000 and 2002 (Sexton et al. 2006).

Contaminated groundwater serves as a source for vapor intrusion of trichloroethylene into homes and is a notable exposure route (Geng et al. 2010; Johnston and MacDonald Gibson 2011). Seventeen monitoring wells at a former chemical works site that operated between 1970 and 2004 had levels as high as 1,220 mg/L (ppm) of trichloroethylene in one well, 14.8 mg/L (ppm) in another well, and <0.2 mg/L (ppm) in all of the other wells. It was reported that exposure levels of trichloroethylene for child residents from indoor air was 2.5 mg/m^3 (460 ppb) which was 2 orders of magnitude higher than outdoor air levels. However, exposure for school children was higher in the outdoor air. In addition, for point source construction workers, the concentration of trichloroethylene in outdoor air was $3.2x10^{-4}$ mg/m^3 ($5.9x10^{-2}$ ppb) (Geng et al. 2010).

Information on trichloroethylene levels in tissue, neonatal blood, cord blood, and meconium fluid is not available.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Because of the pervasiveness of trichloroethylene in the environment, most people are exposed to it through drinking water, air, or food, although the levels of exposure are probably far below those causing

any adverse effects. Concern may be justified, however, for people who are continuously exposed to elevated levels, such as residents of some urban or industrialized areas, people living near waste facilities, or people exposed at work. Short-term exposure to high levels of trichloroethylene may also pose risks for people using products containing the chemical in areas with inadequate ventilation. The discontinuation of trichloroethylene use in many medical applications and some consumer products has generally decreased the exposure risks in these situations.

As a result of volatilization, significantly elevated indoor air levels of trichloroethylene can occur in homes that use water supplies contaminated with trichloroethylene (Andelman 1985a). The transfer of trichloroethylene from shower water to air in one study had a mean efficiency of 61%, which was independent of water temperature (McKone and Knezovich 1991). The study authors concluded that showering for 10 minutes in water contaminated with trichloroethylene could result in a daily exposure by inhalation comparable to that expected by drinking contaminated tap water. Another study using a model shower system found that, in addition to shower spray, shower water collecting around the drain could be an important source of volatilized trichloroethylene, and the fraction volatilized could be affected by spray drop size and flow rate (Giardino et al. 1992). Significantly elevated indoor air levels of trichloroethylene can occur via vapor intrusion, a process whereby trichloroethylene evaporates from contaminated groundwater and soil and migrates into air spaces beneath buildings to enter the indoor air (EPA 2002).

ATSDR has estimated that as many as 1 million military and civilian staff and their families might have been exposed to trichloroethylene and other chlorinated solvents in contaminated drinking water during a period dating back to the 1950s (ATSDR 2017b). Due to a lack of monitoring data at this site prior to the 1980s, the extent and duration of exposure were unknown.

A survey of 20 brands of typographical correction fluids found that several contained ≤10% trichloroethylene, although other volatile organic compounds present at higher levels probably posed a greater hazard to people using these products (Ong et al. 1993). Various other consumer products have been found to contain trichloroethylene, such as paint removers, strippers, adhesives, and lubricants (EPA 1987j).

Workers involved in the manufacture or use of trichloroethylene as a metal degreaser or general solvent may constitute a group at risk because of the potential for occupational exposure. Occupational exposure

to trichloroethylene may also occur during its use as a chemical intermediate in the production of polyvinyl chloride (McNeill 1979).

An EPA Total Exposure Assessment Methodology (TEAM) study conducted in New Jersey attempted to identify factors associated with risk of higher inhalation of trichloroethylene (Wallace et al. 1986b). The following factors (in order of importance) were identified: wood processing, working at a plastics plant, exposure to a gas furnace, working at a scientific lab, and smoking.

EPA (2014a) recently completed a chemical risk assessment for trichloroethylene use in degreasing operations, cleaning, and arts and crafts usage. EPA (2014a) identified cancer risk concerns and short-term and long-term noncancer risk for workers and occupational bystanders at small commercial degreasing facilities that use trichloroethylene-based solvents and dry cleaning facilities that use trichloroethylene-based spotting agents. EPA (2014a) also identified short-term noncancer risks for consumers and residential bystanders from the use of trichloroethylene-containing solvent degreasers and spray-applied protective coatings.

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 trichloroethylene 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 trichloroethylene.

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 trichloroethylene are well characterized (HSDB 2013; McNeill 1979; Windholz 1983) and allow prediction of the

environmental fate of the compound. Estimates based on available constants are generally in good agreement with experimentally determined values. No additional studies are required at this time.

Production, Import/Export, Use, Release, and Disposal. Humans are at risk of exposure to trichloroethylene because of its widespread use and distribution in the environment. Production, import, and use of the chemical are known to be relatively high, but recent quantitative data were not available (HSDB 2013). Trichloroethylene is released to the atmosphere mainly through its use in vapor degreasing operations (EPA 1985e). Landfills can be a concentrated source of trichloroethylene on a local scale. It is also released to surface water and land in sewage sludges and industrial liquid or solid waste. Trichloroethylene is considered a hazardous waste and its disposal is subject to regulations (see Chapter 8). More current data on production, use in food processing and consumer products, releases, efficiency of disposal practices, adequacy of current disposal regulations, and the extent of recovery and recycling of trichloroethylene would assist in estimating human potential exposures, particularly of populations living near industrial facilities and hazardous waste sites.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The TRI, which contains this information for 2017, became available in 2018. This database is updated yearly and should provide a list of industrial production facilities and emissions.

Environmental Fate. Trichloroethylene released to environment partitions mainly to the atmosphere (EPA 1985e). The compound is transported in atmosphere, groundwater, and soil. Trichloroethylene is transformed in the atmosphere by photooxidation (Singh et al. 1982). Trichloroethylene is expected to volatilize very rapidly from surface water and soil (EPA 1985c; Park et al. 1988). Trichloroethylene is biodegraded in water (Jensen and Rosenberg 1975; Smith and Dragun 1984) and, to a limited extent, in soil (Maymo-Gatell et al. 1997; Yagi et al. 1992). Trichloroethylene may persist in groundwater. Additional information on the anaerobic degradation of trichloroethylene in groundwater and on the rates of transformation in soil is needed to define the relative importance of these media as potential pathways for human exposure.

Bioavailability from Environmental Media. Trichloroethylene can be absorbed following inhalation (Andersen et al. 1980; Astrand and Ovrum 1976; Bartonicek 1962; Dallas et al. 1991; Fernandez et al. 1977; Monster et al. 1976; Müller et al. 1974; Sato and Nakajima 1978), oral (DeFalque 1961; D'Souza et al. 1985; Kleinfeld and Tabershaw 1954; Prout et al. 1985; Stephens 1945; Stevens et

al. 1992; Templin et al. 1993; Withey et al. 1983), or dermal (Bogen et al. 1992; Jakobson et al. 1982; McCormick and Abdel-Rahman 1991; Sato and Nakajima 1978; Stewart and Dodd 1964; Tsuruta 1978) exposure. All of these routes of exposure may be of concern to humans because of the potential for trichloroethylene to contaminate the air, drinking water, food, and soil. More information on the absorption of trichloroethylene following ingestion of contaminated soil and plants grown in contaminated soil near hazardous waste sites are needed to determine bioavailability of the compound in these media.

Food Chain Bioaccumulation. Information is available regarding bioaccumulation potential in aquatic food chains. Studies show that trichloroethylene has a low-to-moderate bioconcentration potential in aquatic organisms (Pearson and McConnell 1975) and some plants (Schroll et al. 1994). Information is needed, however, regarding bioaccumulation potential in terrestrial food chains.

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

Trichloroethylene is widely distributed in the environment and has been detected in air (EPA 1982d; Bruckmann et al. 1988; Class and Ballschmiter 1986; Fabian 1986; Harkov et al. 1985; Hartwell et al. 1985; Hov et al. 1984; Kawata and Fujieda 1993; Ligocki et al. 1985; Sullivan et al. 1985), water (Barkley et al. 1980; Burmaster 1982; Ligocki et al. 1985; Mumtaz et al. 1994; Murray and Riley 1973; Otson et al. 1982; Sauer 1981), soil (Hewitt and Shoop 1994; Hunter and Bromberg 1982), and food (Entz and Hollifield 1982; Entz et al. 1982; Grob et al. 1990; Heikes and Hopper 1986; McConnell et al. 1975). The levels of trichloroethylene in air, water, sediment, and foods are well documented, but some of these studies are not current. More recent data characterizing the concentration of trichloroethylene in drinking water, soils, and air surrounding hazardous waste sites and on estimates of human intake from these media are needed to assess human exposure to trichloroethylene for populations living near hazardous waste sites.

Exposure Levels in Humans. Trichloroethylene has been detected in human body fluids such as blood (Brugnone et al. 1994; Skender et al. 1994) and breast milk (Pellizzari et al. 1982). Most of the monitoring data have come from occupational studies of specific worker populations exposed to

trichloroethylene. Mean TWA concentrations generally ranging from ≤50 to 100 ppm have been reported (NCI 1985). More recent monitoring of trichloroethylene levels in air from occupational settings within the United States are needed to determine whether this range is currently relevant. More information on exposure levels for populations living in the vicinity of hazardous waste sites is also needed for estimating human exposure. This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Limited data are available regarding the exposures of children to trichloroethylene. Pellizzari et al. (1982) report detection of trichloroethylene in breast milk and Sexton et al. (2005, 2006) report levels of trichloroethylene measured in the blood of children from the Minneapolis, Minnesota area. Additional information regarding the levels of trichloroethylene in these and other matrices, such as tissue, neonatal blood, cord blood, and meconium fluid, would be helpful in assessing the exposure of children to this substance. Child health data needs relating to susceptibility are discussed in Section 3.12.2, Identification of Data Needs: Children's Susceptibility.

6.8.2 Ongoing Studies

As part of the National Health and Nutrition Examination Survey (NHANES), the Division of Laboratory Sciences in the National Center for Environmental Health, Centers for Disease Control, continues to analyze human blood samples for trichloroethylene and other volatile organic compounds. These data provide estimates regarding frequency of occurrence and background levels of these compounds in the general population.

ATSDR (2011b) is conducting a survey of more than 300,000 people who lived or worked at Camp Lejeune or Camp Pendleton in the 1970s and 1980s. Additional information regarding this survey is available at the following website: http://www.atsdr.cdc.gov/sites/lejeune/health_survey.html.

Other ongoing studies pertaining to trichloroethylene have been identified and are shown in Table 6-10.

Table 6-10. Ongoing Studies on Trichloroethylene

Principal investigator	Study topic	Institution	Sponsor
Smith, MT	Techniques for detection, assessment, and evaluation of human health effects of hazardous substances, including trichloroethylene	University of California Berkeley	National Institute of Environmental Health Sciences

Source: RePORTER 2018

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7. ANALYTICAL METHODS

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

Several methods are available for the analysis of trichloroethylene in biological media. The method of choice depends on the nature of the sample matrix; cost of analysis; required precision, accuracy, and detection limit; and turnaround time of the method. The main analytical method used to analyze for the presence of trichloroethylene and its metabolites, trichloroethanol and TCA, in biological samples is separation by gas chromatography (GC) combined with detection by mass spectrometry (MS) or electron capture detection (ECD) (Delinsky et al. 2005). Trichloroethylene and/or its metabolites have been detected in exhaled air, blood, urine, breast milk, and tissues. A head-space in-tube extraction GC/MS method was developed for detection of volatile low molecular weight compounds in blood and/or urine samples. Tenax® adsorbent resin is used for adsorption and porous, open tubular GC is employed for separation (Rasanen et al. 2010). Details on sample preparation, analytical method, and sensitivity and accuracy of selected methods are provided in Table 7-1.

Several studies have analyzed breath samples for trichloroethylene. Preconcentration on Tenax®-GC cartridges, followed by thermal desorption onto a cryogenic trap connected to the gas chromatograph, was used to analyze exhaled air in several TEAM studies (Wallace et al. 1986a, 1986b, 1986c, 1986d). Vapors were thermally released directly onto the gas chromatograph column for separation and detection by electron impact mass spectrometry (EIMS). A similar study analyzed for trichloroethylene in expired air by directly injecting a portion of the collected sample from a Tedlar® bag into a gas chromatograph equipped with an ECD (Monster and Boersma 1975). Sensitivity was better with GC/MS, but precision

Table 7-1. Analytical Methods for Determining Trichloroethylene in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Exhaled air	Collected in Tedlar® bag; injected into GC	GC/ECD (both trichloro-ethylene and trichloro-ethanol)	5 ppb (trichloro-ethylene); 2 ppb (trichloro-ethanol)	Not reported	Monster and Boersma 1975
Exhaled air	Collected on Tenax®-GC, thermally desorbed; injected into GC	HRGC/MS	0.3 ppb	95–99	Wallace et al. 1986a
Blood	Blood transferred to a pre-weighed SPME headspace vial using a 2-mL pre-cleaned glass syringe, agitated, and then transferred to the GC injection port	(SPME-GC–MS/MS	0.027 µg/L	78–99	Aranda-Rodriguez et al. 2015
Blood	Digested with H_2SO_4: dimethyl sulfate at 60°C for 4 hours; headspace gas injected into GC	GC/ECD (trichloro-ethylene, trichloro-ethanol, and trichloro-acetic acid)	3 ppb (trichloro-ethylene); 60 ppb (trichloro-ethanol); 30 ppb trichloro-acetic acid)	Not reported	Monster and Boersma 1975
Blood	Thermally decarboxylated; subjected to static headspace analysis	GC/ECD (for metabolite TCA)	2 ppb	101–109	Ziglio et al. 1984
Blood	Enzyme hydrolysis of sample; decarboxy-lation of TCA; headspace gas analyzed	GC/ECD	20 ppb	95 (trichloro-ethanol); 102 (trichloro-ethanol); 94 (TCA)	Christensen et al. 1988
Blood, plasma, and serum	Sample in sealed vial subjected to static headspace analysis	GC/ECD	100 ppb	Not reported	Ramsey and Flanagan 1982
Urine	Thermally decarboxy-lated; reacted with pyridine	Spectro-photometry (for metabolite TCA)	<800 ppb	93.5	Pekari and Aitio 1985a
Urine	Enzyme hydrolysis of sample; decarboxy-lation of TCA; headspace gas analyzed	GC/ECD	20 ppb	96 (trichloro-ethanol); 98 (TCA)	Christensen et al. 1988

Table 7-1. Analytical Methods for Determining Trichloroethylene in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Urine	Hydrolyzed with H_2SO_4; extracted with isooctane; injected into GC	GC/ECD (for metabolite trichloro-ethanol)	75 ppb	98.2	Pekari and Aitio 1985b
Tissue	Mixed with a proteolytic enzyme; incubated at 65°C; headspace gas analyzed	GC/ECD	Not reported	Not reported	Ramsey and Flanagan 1982
Tissue	Homogenized with saline and isooctane at 4°C; headspace gas analyzed	GC/ECD	8.4 ppb	86–91	Chen et al. 1993
Liquid, solid, and oily matrices including animal tissues	Water added to the sample (soil, tissue, or oil), followed by vacuum distillation and cryogenic trapping	VD/GC/MS (Method 8261)	–	–	EPA 2007h
Human milk	Purged warm; trapped in Tenax®-GC; thermally desorbed	HRGC/MS	Qualitative identification	Not reported	Pellizzari et al. 1982

ECD = electron capture detector; GC = gas chromatography; HRGC = high-resolution gas chromatography; H_2SO_4 = sulfuric acid; MS = mass spectrometry; SPME-GC–MS/MS = solid-phase microextraction gas chromatography coupled with isotope-dilution mass spectrometry in selected reaction monitoring mode; TCA = trichloroacetic acid

was greater with GC/ECD. No recovery data were given for the GC/ECD technique, so accuracy could not be compared. GC/ECD was also used to measure trichloroethanol, a metabolite of trichloroethylene, in expired air (Monster and Boersma 1975). The sensitivity and precision were comparable to that of trichloroethylene measurement.

The method most frequently used to determine the presence of trichloroethylene or its metabolites in biological tissues and fluids is headspace analysis, followed by GC/MS or GC/ECD (Christensen et al. 1988; Monster and Boersma 1975; Pekari and Aitio 1985a, 1985b; Ziglio et al. 1984). In headspace analysis, the gaseous layer above the sample is injected into the gas chromatograph. Headspace gases can be preconcentrated prior to GC analysis (Michael et al. 1980) or injected directly into the gas chromatograph (Collins et al. 1986; Ramsey and Flanagan 1982). Analysis of blood and urine for the trichloroethylene metabolites TCA, trichloroethanol, and trichloroethanol-β-glucuronide has been done primarily by headspace GC/ECD (Christensen et al. 1988). Trichloroethanol-β-glucuronide in the samples was first hydrolyzed to trichloroethanol by β-glucuronidase; TCA was then decarboxylated to chloroform. A headspace sample was then analyzed for trichloroethanol and chloroform. The method had relatively high accuracy and acceptable precision. Detection limits were generally in the low-ppb range. Whole-tissue analysis has been performed by GC/ECD after enzyme treatment (Ramsey and Flanagan 1982) and after homogenization in the presence of an extractive solvent (Chen et al. 1993). A method that measures biomarkers of exposure to VOC parent compounds such as trichloroethylene has been reported. The trichloroethylene, metabolite N-acetyl-S-(1,2-dichlorovinyl)-L-cysteine, has been effectively quantified in urine using ultra high performance liquid chromatography coupled with electrospray ionization tandem mass spectrometry (UPLC-ESI/MSMS) (Alwis et al. 2012).

Purge-and-trap methods have also been used to analyze biological fluids for the presence of trichloroethylene. Breast milk and blood were analyzed for trichloroethylene by purging onto a Tenax® gas chromatograph to concentrate the volatiles, followed by thermal desorption and analysis by GC/MS (Antoine et al. 1986; Pellizzari et al. 1982). However, the breast milk analysis was only qualitative, and recoveries appeared to be low for those chemicals analyzed (Pellizzari et al. 1982). Precision (Antoine et al. 1986) and sensitivity (Pellizzari et al. 1982) were comparable to headspace analysis. Quantitative analysis of trichloroethylene in breast milk is performed using GC/MS after the samples undergo homogenization, lipid hydrolysis, centrifugation, and extraction. The methods limit of detection is 1.5 ng/mL (Beamer et al. 2012).

Additional information regarding methods for monitoring trichloroethylene in biological samples is available in the CDC Fourth National Report on Human Exposure to Environmental Chemicals (CDC 2018).

7.2 ENVIRONMENTAL SAMPLES

Analysis of environmental samples is similar to that of biological samples. The most common methods of analyses are GC coupled to MS, ECD, a Hall's electrolytic conductivity detector (HECD), or a flame-ionization detector (FID) (Delinsky et al. 2005). Preconcentration of samples is usually done for air by sorption on a solid sorbent and by the purge-and-trap method for liquid and solid matrices. Alternatively, headspace above liquid and solid samples may be analyzed without preconcentration. Details of commonly used analytical methods for several types of environmental samples are presented in Table 7-2.

The primary methods of analyzing for trichloroethylene in air are GC combined with MS and GC with ECD. Air samples are usually pumped through a sample collection column, with Tenax®-GC and coconut charcoal, the most common adsorbents. Trichloroethylene is thermally desorbed from the collection column and concentrated on a cryogenic trap column located on the gas chromatograph. Vapors are heat-released from the trapping column directly to the gas chromatograph (Krost et al. 1982; Wallace et al. 1986a, 1986b, 1986c, 1986d). Grab-samples of air can also be obtained and preconcentrated on a cryogenic column (Makide et al. 1979; Rasmussen et al. 1977). The limit of detection for both GC/ECD and GC/MS is in the low- to sub-ppb range (Krost et al. 1982; Makide et al. 1979; Rasmussen et al. 1977; Wallace et al. 1986a, 1986d). With careful technique, precision for both is acceptable (Krost et al. 1982; Rasmussen et al. 1977; Wallace et al. 1986a, 1986b, 1986c, 1986d). Accuracy of the two analytical methods could not be compared because no recovery data were located for GC/ECD. NIOSH Methods 3071 and 1022 describe techniques for detection of trichloroethylene in air which combine GC with photoionization detection (PID) or flame ionization detection (FID) (NIOSH 1994a, 1994b). Sample detection limits are in the low ppm range. The detection and measurement of trichloroethylene in air can also be adequately performed using infrared spectrometry instead of GC (Xiao et al. 1990). EPA Method 0031is used to analyze and prepare VOCs, such as trichloroethylene, in gaseous emissions from stationary sources such as hazardous waste incinerators. The concentration of each compound in the emission should not exceed the upper concentration limit of 1.5 ppm. The target detection limit is 0.1 μg/m³ (ng/L) (EPA 1996c). Improvements in the sensitivity of analytical methods for volatile chlorinated hydrocarbons in air have been reported by Zoccolillo et al. (2010). The method is based on cryofocusing trap injection combined with GC/MS. The detection limit for trichloroethylene

Table 7-2. Analytical Methods for Determining Trichloroethylene in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Sample is collected using Tedlar bags and a flow rate of 0.02–0.05 L/minute or higher	Portable GC/PID (Method 3701)	0.1 ppm	—	NIOSH 1994b
Air	Sample is collected using a solid sorbent tube with coconut shell charcoal and a flow rate of 0.01–0.2 L/minute	GC/FID (Method 1022)	27 ppm	92–94	NIOSH 1994a
Air	Collected in stainless steel canister; preconcentrated in cooled adsorbent; thermally desorbed	GC/ECD	1 ppt	Not reported	Makide et al. 1979
Air	Adsorbed on Tenax®-GC thermally desorbed to on-column cold trap; heat-released	HRGC/MS	1.9 ppt	Not reported	Krost et al. 1982
Air	Collected in stainless steel canister; preconcentrated by cryogenic trapping; thermally desorbed	GC/ECD	0.3 ppt	Not reported	Rasmussen et al. 1977
Air	Adsorbed on Tenax®-GC; thermally desorbed to on-column cold trap; heat-released	HRGC/MS	15 ppt	95–99	Wallace et al. 1986a
Air	Collected in canisters with a diaphragm pump; cryofocusing trap injection	GC/MS	0.1 pptv	—	Zoccolillo et al. 2010
Effluent gas	Sampling is done using a heated glass-lined probe with an isolation valve, charcoal trap, and water cooled glass condenser; adsorption is on a set of Tenax®-GC traps and an Anasorb®-747 trap	GC/MS (Method 0031)	0.1 μg/m³	—	EPA 1996c
Water	Sample is purged and trapped and then thermally desorbed	GC/PID (Method 502.2)	0.3–0.5 ppb	97–101	EPA 1995a
Water	Sample is purged and trapped and then thermally desorbed	GC/ELCD (Method 502.2)	0.02–0.04 ppb	96–98	EPA 1995a

Table 7-2. Analytical Methods for Determining Trichloroethylene in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water	Sample is purged and trapped and then thermally desorbed	Preparation only (Method 5030C)	—	—	EPA 2003
Water	Sample is purged and trapped and then thermally desorbed	GC/MS (Method 524.2)	0.02–0.19 ppb	90–106	EPA 1995b
Water	Headspace-free samples collected in amber glass vials with polytetrafluoroethylene-faced septa, purged and trapped, and then thermally desorbed	GC/MS (Method 524.3)	0.035 ppb	91.6–107	EPA 2009b
Water	Sample is extracted using methyl tert-butyl ether or pentane and injected into the GC column	GC/ECD (Method 551.1)	0.002–0.042 ppb	93–101	EPA 1995c
Water	Sample is purged and trapped and then thermally desorbed	GC/MS (Method 6200B)	0.045 ppb	105	APHA 1998a
Water	Sample is purged and trapped	GC/ECD (Method 6200C)	0.012 ppb	80	APHA 1998b
Water	Sample is purged and trapped	GC/PID (Method 6200C)	0.014 ppb	57	APHA 1998b
Water	Sample is purged and trapped and then thermally desorbed	GC/MS (Method O-3115)	3 ppb	70–130	USGS 1987
Water	Sample is purged and trapped and then thermally desorbed	GC/MS (Method O-4127-96)	0.028 ppb	92.1–111	USGS 1998
Water	Purged and trapped on Tenax®-GC; thermally desorbed	HRGC/HSD	0.5 ppb	91	APHA 1985
Water	Purged and trapped on coconut charcoal/Tenax®/silica gel; thermally desorbed	GC/MS	1.9 ppb	101	EPA 1982b, 1982e
Water	Purged and trapped on coconut charcoal/Tenax®/silica gel; thermally desorbed	GC/HSD	0.12 ppb	106	EPA 1982b, 1982e

Table 7-2. Analytical Methods for Determining Trichloroethylene in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water	Equilibrated in sealed vial at room temperature; headspace gas injected into GC	GC/ECD	0.04 ppb	105	Dietz and Singley 1979
Water	Purged at room or elevated temperature; trapped in closed loop; injected into GC	GC/ECD	0.2 ppb	104	Wang and Lenahan 1984
Water	Purged and trapped on Tenax®-GC; thermally desorbed	GC/HECD; GC/FID	<0.1 ppb (HECD); 0.1 ppb (FID)	98 (HECD); 79 (FID)	Otson and Williams 1982
Water	Purged and trapped on Tenax®-GC; thermally desorbed	GC/HECD	0.05 ppb	50–90	Wallace et al. 1986a
Water	Sample directly injected	GC/UV	1 ppb	39	Motwani et al. 1986
Waste water (municipal and industrial discharges)	Sample is purged and trapped with direct aqueous injection; then thermally desorbed onto column	GC/ECD or MCD (Method 601)	0.12 ppb	87	EPA 2001a
Waste water (municipal and industrial discharges)	Sample is purged and trapped; the trap is backflushed and heated to desorb compounds onto column	GC/MS (Method 624)	4.1 ppb	104	EPA 2010c
Water/Waste water	Grab sample is collected in glass containers, purged and trapped with isotopic dilution, and then thermally desorbed	GC/MS (Method 1624)	10 ppb/10 μg/L	Labeled compound recovery: 35–196	EPA 2007a
Groundwater, aqueous sludges, caustic liquors, soils, sediments	Purge-and-trap (EPA Method 624) or direct injection (EPA Method 5030)	GC/MS	5 μg/L (groundwater; 5 μg/kg (soil/sediment)	71–157%	EPA 1994c
Groundwater, surface water, waste water	Purge-and-trap (EPA Method 624) or direct injection (EPA Method 5030)	GC with electrolytic conductivity detector (HECD)	0.001 μg/L	35–146	EPA 1994b Method 8010B

Table 7-2. Analytical Methods for Determining Trichloroethylene in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Soil	Equilibrated in sealed vial; headspace gas injected into GC	GC/PID	100 ppb	Not reported	Hewitt et al. 1992
Soil	Equilibrated in sealed vial; headspace gas injected into GC	GC/FID	Not reported	80	Pavlostathis and Mathavan 1992
Solid waste	Sample can be directly injected or prepared by purge and trap, headspace, or vacuum distillation	GC/PID (Method 8021B)	0.2 ppb	100	EPA 1996a
Solid waste	Sample can be directly injected or prepared by purge and trap, headspace, or vacuum distillation	GC/HECD (Method 8021B)	0.1 ppb	96	EPA 1996a
Soils/ sediments and solid waste	Samples collected in crimp-seal or screw-top headspace vial, preserved and fortified, rotated for diffusion, equilibrated and mixed; headspace gas is forced into GC by pressurizing with helium (Method 5021)	GC/MS (Method 8260B)	0.1–3.4 µg/kg		EPA 1996b 1996d
Solid waste	Sample can be directly injected or prepared by purge and trap, headspace, or vacuum distillation (EPA Methods 5030/5035, 5032, 5041)	GC/MS (Method 8260B)	—	—	EPA 1996b; 1996e, 1996f, 1996g, 1996h
Liquid and solid waste	Equilibrated in sealed vial; headspace gas injected into GC	GC/HSD	0.03 ppb	106	EPA 1982c
Building materials and consumer products[a]	Collected by adsorption onto sorbent; thermally desorbed	HRGC/MS	0.02 ppt	Not reported	Wallace et al. 1987
Food	Undigested or H_2SO_4-digested samples at 90°C subjected to static headspace analysis	HRGC/ECD; GC/MS	0.23 ppb	90–100	Entz and Hollifield 1982

Table 7-2. Analytical Methods for Determining Trichloroethylene in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Food	Extraction with isooctane; clean-up on Florisil column if needed	GC/ECD; GC/HECD	6 ppb (GC/ECD); 13 ppb (GC/HECD)	>50	Daft 1988
Grains, grain-based foods	Purged and trapped on Tenax®/XAD-4 resin; desorb with hexane	GC/ECD	Low- to sub-ppb	86–100	Heikes and Hopper 1986
Liquid, solid, and oily matrices including animal tissues	Water is added to the sample (soil, tissue, or oil); followed by vacuum distillation and cryogenic trapping (Method 5023)	VD/GC/MS (Method 8261)	—	—	EPA 1996e, 2007

[a]Sample is air from an environmental chamber containing the building material or consumer product.

ECD = electron capture detector; ELCD = electrolytic conductivity detector; FID = flame ionization detection; GC = gas chromatography; HECD = Hall electrolytic conductivity detector; HRGC = high-resolution gas chromatography; HSD = halogen-specific detector; H_2SO_4 = sulfuric acid; MS = mass spectrometry; PID = photo ionization detection; pptv = parts per trillion by volume; USGS = United States Geological Survey; UV = ultraviolet detection; VD = vacuum distillation

was reported as 0.1 parts per trillion by volume (pptv). A novel method for the detection of trichloroethylene in indoor air, in the presence of multiple interferences, is reported by Kim et al. (2011, 2012). The method involves a micro-fabricated GC and microsensor array detection. The limit of detection for the sensors used range from 0.8 to 2.4 ppb in a 1-L sample and from 0.04 to 0.12 ppb in a 20-L sample (Kim et al. 2011, 2012).

Trichloroethylene can be detected in drinking water, groundwater, waste water, and leachate from solid waste. In most methods, trichloroethylene is liberated from the liquid matrix by purging with an inert gas and concentrated by trapping on a suitable solid sorbent. Trichloroethylene is thermally desorbed and backflushed onto the gas chromatograph column with an inert gas. Detection of trichloroethylene is generally by HECD (or other halogen-specific detector) or MS (APHA 1985, 1998a, 1998b; EPA 1982b, 1982c, 1982e, 1995a, 1995b, 1995c, 2001a, 2001c,2007a, 2009b; Otson and Williams 1982; USGS 1987, 1998; Wallace et al. 1986a, 1986c, 1986d). The limit of detection is in the sub-ppb range for halogen-specific detectors (APHA 1985; EPA 1982b, 1982c, 1982e) and in the low-ppb range for MS (EPA 1982b, 1982e). An experiment with a purge-closed loop sample extraction system, followed by GC/ECD, GC/HECD, or GC/FID analysis, yielded a sensitivity and reproducibility comparable to headspace analysis (Otson and Williams 1982; Wang and Lenahan 1984).

Headspace analysis has also been used to determine trichloroethylene in water samples. High accuracy and excellent precision were reported when GC/ECD was used to analyze headspace gases over water (Dietz and Singley 1979). Direct injection of water into a portable GC suitable for field use employed an ultraviolet detector (Motwani et al. 1986). While detection was comparable to the more common methods (low ppb), recovery was very low. Solid waste leachates from sanitary landfills have been analyzed for trichloroethylene and other volatile organic compounds (Schultz and Kjeldsen 1986). Detection limits for the procedure, which involves extraction with pentane followed by GC/MS analysis, are in the low-ppb and low-ppm ranges for concentrated and unconcentrated samples, respectively. Accuracy and precision data were not reported.

Analysis of soils and sediments is typically performed with aqueous extraction followed by headspace analysis or the purge-and-trap methods described above. Comparison of these two methods has found them equally suited for on-site analysis of soils (Hewitt et al. 1992). The major limitation of headspace analysis has been incomplete desorption of trichloroethylene from the soil matrix, although this was shown to be alleviated by methanol extraction (Pavlostathis and Mathavan 1992). A head-space method using helium to force the gas into the GC reports detection limits of 0.1–3.4 μg/kg (EPA 1996B).

Several procedures for determination of trichloroethylene in food were located. GC/ECD and GC/halogen-specific detector (HSD) are most commonly used to analyze solid samples for trichloroethylene contamination. Extraction, purge-and-trap, and headspace analysis have all been used to prepare samples. Analysis of headspace gases by GC coupled with ECD, MS, or HSD has proven relatively sensitive (low- to sub-ppb range) and reproducible for a variety of foods (Entz and Hollifield 1982; EPA 1982b, 1982e). GC/MS has also been used to analyze building materials and consumer products (Wallace et al. 1987). GC/HSD of headspace gases is the EPA-recommended method for solid matrices (EPA 1982c). Foods have also been analyzed for trichloroethylene by GC/ECD/HECD following isooctane extraction. Sensitivity was comparable to headspace methods, but recovery (>50%) and precision (18–59%) were not as good (Daft 1988). In both preparation techniques, increased lipid content of the matrix adversely affected accuracy and precision. A purge-and-trap technique proved useful for analyzing grains and grain-based foods with high sensitivity and good recovery (Heikes and Hopper 1986).

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 trichloroethylene 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 trichloroethylene.

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. Methods are available for monitoring exposure to trichloroethylene by measuring trichloroethylene in breath and blood; trichloroethanol in breath, blood, and urine; and TCA in blood and urine (Christensen et al. 1988; Monster and Boersma 1975; Pellizzari et al. 1982; Ramsey and Flanagan 1982; Wallace et al. 1986a, 1986b, 1986c, 1986d). Available methods are sensitive for measuring levels of trichloroethylene and its metabolites at which health effects have been observed to occur, for example, in workers known to be overexposed to trichloroethylene (Christensen et al. 1988; Monster and Boersma 1975; Ziglio et al. 1984). These methods have also been used to measure background levels of trichloroethylene and its metabolites in individuals believed not to have been exposed to higher-than-expected levels of trichloroethylene (e.g., office workers and housewives). The methods are generally reliable, although increased precision for most methods would increase reliability. However, trichloroethylene is pervasive in the environment, and background levels for the general population are ill defined. Levels may vary considerably within the environment, making it difficult to differentiate between normal background exposure and excess exposure. Further research on the relationship between levels found in living environments and levels found in biological media would help in better defining background levels of the chemical. This would also aid in determining if improved methods of monitoring exposure are needed.

Effect. Improved methods of tissue analysis, giving greater sensitivity and reproducibility, would help in determining the quantitative relationship between observed toxic effect on specific organs and levels of trichloroethylene in these organs. Trichloroethylene is known to affect the kidney. To determine the potential for human kidney damage resulting from workplace air exposure to trichloroethylene, urinary total protein and β2-microglobulin can be measured. To detect renal glomerular dysfunction, urinary total protein is analyzed by the Coomassie blue dye binding method using a protein assay. To detect renal tubular dysfunction, an enzyme immunoassay is used to measure β2-microglobulin (Nagaya et al. 1989b).

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Existing methods for determining trichloroethylene in air and water, the media of most concern for human exposure, are sensitive, reproducible, and reliable for measuring background levels in the environment (see Table 7-1). These methods can also be used to measure levels of trichloroethylene and its metabolites at which health effects occur. Research investigating the relationship between levels

measured in air and water and observed health effects could increase our confidence in existing methods and/or indicate where improvements are needed. Methods for solid matrices vary in accuracy and precision depending on the method and the matrix (e.g., sludge, soil, sediment, building material). No detailed descriptions of methods specifically for soil were located. Soil analyses presumably were done using a method for solid waste (e.g., EPA Method 8010). Data specifically for soil might be useful in evaluating the reliability of soil data and in determining if additional methods are needed. Improved methods of detecting trichloroethylene in plants and foods, especially those with higher fat content, would aid in determining the contribution of trichloroethylene exposure from these sources. This would be especially important in determining the potential for contamination of populations living adjacent to hazardous waste sites and other potential sources of exposure to higher than background levels of trichloroethylene.

7.3.2 Ongoing Studies

The Division of Laboratory Sciences at the National Center for Environmental Health, Centers for Disease Control and Prevention continues to develop and refine methods for the analysis of trichloroethylene and other volatile organic compounds in blood (CDC 2018). These methods use purge and trap methodology, high-resolution gas chromatography, and magnetic sector mass spectrometry, which give detection limits in the low parts per trillion (ppt) range.

8. REGULATIONS, ADVISORIES, AND GUIDELINES

MRLs are substance-specific estimates that are intended to serve as screening levels. They are used by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites.

The chronic-duration oral MRL of 0.0005 mg/kg/day was based on the results of three oral exposure studies reporting immunological, endocrine, and developmental effects in rats or mice (Johnson et al. 2003; Keil et al. 2009; Peden-Adams et al. 2006) and a PBPK model developed by EPA (2011e), which was used to calculate the idPOD human equivalency doses (HED_{99}).

The ATSDR chronic-duration oral MRL of 0.0005 mg/kg/day was adopted as the ATSDR intermediate-duration oral MRL for trichloroethylene.

The chronic-duration inhalation MRL of 0.0004 ppm was based on the results of two oral exposure studies that reported endocrine and developmental effects in rats and mice (Johnson et al. 2003; Keil et al. 2009) and a PBPK model developed by EPA, which was used to calculate the idPOD and route-to-route extrapolation to human equivalency concentrations (HEC_{99}) for these studies.

The ATSDR chronic-duration inhalation MRL of 0.0004 ppm was adopted as the ATSDR intermediate-duration inhalation MRL for trichloroethylene.

EPA has derived an oral reference dose (RfD) of $5x10^{-4}$ mg/kg/day for chronic exposure to trichloroethylene based on drinking water studies in rats and mice (IRIS 2011).

EPA has derived a chronic inhalation reference concentration (RfC) of 0.002 mg/m^3 (0.0004 ppm) for chronic exposure to trichloroethylene based on drinking water studies in rats and mice (IRIS 2011).

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

Table 8-1. Regulations and Guidelines Applicable to Trichloroethylene

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	Group 1[a]	IARC 2014
WHO	Air quality guidelines[b]	2.3 μg/m^3	WHO 2010
	Drinking water quality guidelines	0.02 mg/L[c]	WHO 2011
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)	10 ppm	ACGIH 2012
	STEL	25 ppm	
AIHA	ERPG-1[c,d]	100 ppm	AIHA 2011
	ERPG-2[c]	500 ppm	
	ERPG-3[c]	5,000 ppm	
DOE	PAC-1[e]	130 ppm	DOE 2012
	PAC-2[e]	450 ppm	
	PAC-3[e]	3,800 ppm	
EPA	AEGL-1[f]		EPA 2013c
	10-minutes	260 ppm	
	30-minutes	180 ppm	
	60-minutes	130 ppm	
	4-hours	84 ppm	
	8-hours	77 ppm	
	AEGL-2[f]		
	10-minutes	960 ppm	
	30-minutes	620 ppm	
	60-minutes	450 ppm	
	4-hours	270 ppm	
	8-hours	240 ppm	
	AEGL-3[f]		
	10-minutes	6,100 ppm	
	30-minutes	6,100 ppm	
	60-minutes	3,800 ppm	
	4-hours	1,500 ppm	
	8-hours	970 ppm	
	Hazardous air pollutant	Yes	EPA 2013d 42 USC 7412
	NAAQS	No data	EPA 2013g

Table 8-1. Regulations and Guidelines Applicable to Trichloroethylene

Agency		Description	Information	Reference
	NIOSH	REL (potential occupational carcinogen)	2 ppm (60-minute ceiling as anesthetic gas) 25 ppm (10-hour TWA for all other exposures)	NIOSH 2013
		IDLH	1,000 ppm (potential occupational carcinogen)	NIOSH 1994c
	OSHA	PEL (8-hour TWA) for general industry	100 ppm	OSHA 2013b 29 CFR 1910.1000, Table Z-2
		Acceptable ceiling concentration	200 ppm	
		Acceptable maximum peak above the acceptable ceiling concentration for an 8-hour shift	300 ppm for 5 minutes in any 2 hours	
		Highly hazardous chemicals	No data	OSHA 2013a 29 CFR 1910.119, Appendix A
b. Water				
	EPA	Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act	Yes	EPA 2012a 40 CFR 116.4
		Drinking water contaminant candidate list	No data	EPA 2009c 74 FR 51850
		Drinking water standards and health advisories		EPA 2012b
		DWEL	0.2 mg/L	
		Cancer risk at 10^{-4}	0.3 mg/L	
		Public health goal	Zero	
		National primary drinking water standards		EPA 2009d
		MCL[g]	0.005 mg/L	
		Public health goal	Zero	
		National recommended water quality criteria: human health for the consumption of (at 10^{-4} risk)		EPA 2009e
		Water + organism	2.5 μg/L	
		Organism only	30 μg/L	
		Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act	No data	EPA 2012d 40 CFR 117.3
	FDA	Allowable trichloroethylene level in bottled water	0.005 mg/L	FDA 2018 21 CFR 165.110

Table 8-1. Regulations and Guidelines Applicable to Trichloroethylene

Agency		Description	Information	Reference
c. Food				
	FDA	EAFUS[h]	Yes	FDA 2013
d. Other				
	ACGIH	Carcinogenicity classification	A2[i]	ACGIH 2012
		BEI (end of shift end of workweek)		
		Trichloroethylene acid in urine	15 mg/L	
		Trichloroethylene in blood (without hydrolysis)	0.5 mg/L	
	EPA	Carcinogenicity classification	Carcinogenic to humans	IRIS 2011
		RfC	0.002 mg/m^3	
		RfD	5x10^{-4} mg/kg/day	
		Oral slope factor	4.6x10^{-2} per mg/kg/day	
		Inhalation unit risk	4.1x10^{-6} per µg/m^3	
		Identification and listing of hazardous waste	U228	EPA 2012c 40 CFR 261, Appendix VIII
		Inert pesticide ingredients in pesticide products approved for nonfood use only	No data	EPA 2013e
		Master Testing List	Yes[j]	EPA 2013f
		RCRA waste minimization PBT priority chemical list	No data	EPA 1998 63 FR 60332
		Standards for owners and operators of hazardous waste TSD facilities; groundwater monitoring list	Yes	EPA 2012e 40 CFR 264, Appendix IX
		Superfund, emergency planning, and community right-to-know		
		Designated CERCLA hazardous substance and reportable quantity pursuant to Section 311(b)(2) of the Clean Water Act, Section 307(a) of the Clean Water Act, Section 112 of the Clean Air Act, and Section 3001 of RCRA	200 pounds	EPA 2012f 40 CFR 302.4
		Effective date of toxic chemical release reporting	01/01/1987	EPA 2012h 40 CFR 372.65
		Extremely hazardous substances and its threshold planning quantity	No data	EPA 2012g 40 CFR 355, Appendix A
		TSCA chemical lists and reporting periods	No data	EPA 2012i 40 CFR 712.30
		TSCA health and safety data reporting	No data	EPA 2012j 40 CFR 716.120

Table 8-1. Regulations and Guidelines Applicable to Trichloroethylene

Agency	Description	Information	Reference
NTP	Carcinogenicity classification	Known to be a human carcinogen	NTP 2016

[a]Group 1: carcinogenic to humans.
[b]The concentration of airborne trichloroethylene associated with an excess lifetime cancer risk of 1 in 1,000,000.
[c]Provisional guideline value due to uncertainties in the health database.
[c]ERPG-1: maximum airborne concentration below which it is believed that nearly all individuals could be exposed for up to 1 hour without experiencing other than mild transient adverse health effects or perceiving a clearly defined, objectionable odor; ERPG-2: maximum airborne concentration below which it is believed that nearly all individuals could be exposed for up to 1 hour without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protective action; ERPG-3: is the maximum airborne concentration below which it is believed that nearly all individuals could be exposed for up to 1 hour without experiencing or developing life-threatening health effects (AIHA 2011).
[d]Odor should be detectable near ERPG-1.
[e]PAC-1: mild, transient health effects; PAC-2: irreversible or other serious health effects that could impair the ability to take protective action; PAC-3: life-threatening health effects (DOE 2012).
[f]AEGL-1: is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, nonsensory effects; however, these effects are not disabling and are transient and reversible upon cessation of exposure; AEGL-2: is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting, adverse health effects or an impaired ability to escape; AEGL-3: is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening adverse health effects or death (EPA 2013c).
[g]Potential health effects from long-term exposure above the MCL could cause liver problems and increased risk of cancer; common sources of contaminant in drinking water include discharges from metal degreasing sites and other factories (EPA 2009d).
[h]The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.
[i]A2: suspected human carcinogen.
[j]Chemical testing program underway and voluntary testing agreement under SIDS for health and ecological effects and chemical fate.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; AIHA = American Industrial Hygiene Association; BEI = biological exposure indices; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; DOE = Department of Energy; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; ERPG = emergency response planning guidelines; FDA = Food and Drug Administration; FR = Federal Register; GRAS = generally recognized as safe; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; NAAQS = National Ambient Air Quality Standards; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PBT = persistent, bioaccumulative, and toxic; PEL = permissible exposure limit; RCRA = Resource Conservation and Recovery Act; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; SIDS = screening information data set; STEL = short-term exposure level; TLV = threshold limit values; TSCA = Toxic Substances Control Act; TSD = treatment, storage, and disposal; TWA = time-weighted average; USC = United States Code; 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 BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

Cancer Effect Level (CEL)—The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study— A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the 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 that must not be exceeded.

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 risk 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)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

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 new cases 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 hazardous substance.

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) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work 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 (insects or other organisms harmful to cultivated plants or animals).

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 blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q_1*—The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually μg/L for water, mg/kg/day for food, and μg/m^3 for air).

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL, from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a hazardous substance. 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 hazardous substance.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, 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)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

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 it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

Toxic Dose$_{(50)}$ (TD$_{50}$)—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic—The absorption, distribution, and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis, 3 being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any substance 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 route and 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 substance-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 and Human Health Sciences, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S102-1, Atlanta, Georgia 30329-4027.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Trichloroethylene
CAS Numbers: 79-01-6
Date: June 2019
Profile Status: Final
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 61, 86
Species: Mouse, Rat

Minimal Risk Level: 0.0004 [ ] mg/kg/day [X] ppm

The ATSDR chronic-duration inhalation MRL of 0.0004 ppm for trichloroethylene was adopted as the ATSDR intermediate-duration inhalation MRL (see chronic-duration inhalation MRL worksheet for more information). The ATSDR chronic-duration inhalation MRL is based, in part, on results of PBPK modeling exercises that simulated 100 weeks of exposure for humans (EPA 2011e). Sample simulations for a 52-week exposure (within the range of an ATSDR-defined intermediate-duration exposure [15–364 days]) resulted in the same internal dose point of departure (idPOD) as the idPOD resulting from simulations for the 100-week exposure.

Agency Contact (Chemical Manager): G. Daniel Todd, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Trichloroethylene
CAS Numbers: 79-01-6
Date: June 2019
Profile Status: Final
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 61, 86
Species: Mouse, Rat

Minimal Risk Level: 0.0004 [ ] mg/kg/day [X] ppm

The chronic-duration inhalation MRL is based on the results of two critical oral exposure studies that reported decreased thymus weight in female mice (Keil et al. 2009) and fetal heart malformations in rats (Johnson et al. 2003). In the EPA assessment for trichloroethylene (EPA 2011e), EPA developed a PBPK model, which was used to calculate the idPOD and perform route-to-route extrapolation to human equivalency concentrations (HECs) for these studies. The resulting HEC_{99} values were 0.033 ppm based on thymus weight and 0.0037 ppm based on fetal heart malformations. The HEC_{99} of 0.033 ppm for thymus weight was divided by a total uncertainty factor of 100 (to account for use of a LOAEL and to account for species extrapolation and human variability using a PBPK model); the resulting candidate chronic RfC was 0.00033 ppm. The HEC_{99} of 0.0037 ppm for fetal heart malformations was divided by a total uncertainty factor of 10 (to account for species extrapolation and human variability using a PBPK model); the resulting candidate chronic RfC was 0.00037 ppm. EPA (2011e) selected the midpoint value of the studies (0.0004 ppm, rounded up from 0.00035 ppm) as the chronic RfC for trichloroethylene. ATSDR agreed that this was a reasonable approach. The resulting chronic-duration inhalation MRL is 0.0004 ppm.

Keil et al. (2009)

Reference: Keil DE, Peden-Adams MM, Wallace S, et al. 2009. Assessment of trichloroethylene (TCE) exposure in murine strains genetically-prone and non-prone to develop autoimmune disease. J Environ Sci Health A Tox Hazard Subst Environ Eng 44(5):443-453.

Experimental design: Groups of 9-week-old female B6C3F1 mice (9–10/group) were administered trichloroethylene in the drinking water at 0, 1,400, or 14,000 ppb (1.4 or 14 ppm) in 1% emulphor vehicle for 30 weeks. During the exposure period, serum levels of total IgG and autoantibodies (anti-ssDNA, -dsDNA, and -glomerular antigen [GA]) were monitored. Body weights were recorded 1 day prior to the initiation of trichloroethylene exposure and again at exposure termination. At sacrifice, the spleen, thymus, liver, and kidneys were weighed. Spleen and thymus were processed for assessment of cell counts and activity. Kidneys were processed for histopathologic evaluation; renal pathology was scored by grading glomerular inflammation, crescent formation, and necrosis in histopathology slides.

Effect noted in study and corresponding doses: Decreased thymus weight (30% lower than controls) and increased serum levels of IgG and selected autoantibodies at 1.4 ppm trichloroethylene in the drinking water (EPA-estimated dose of 0.35 mg/kg/day).

Dose and end point used for MRL derivation: A PBPK model was used to calculate the idPOD (idPOD=0.139 mg trichloroethylene metabolized/$kg^{3/4}$/day) from the applied dose LOAEL of 0.35 mg/kg/day. The mouse idPOD was converted to a HEC_{99} (HEC_{99}=0.033 ppm) for lifetime

continuous exposure derived from combined interspecies, intraspecies, and route-to-route extrapolation using the PBPK model for trichloroethylene.

[ ] NOAEL [ ] LOAEL [X] HEC_{99}

Uncertainty Factors used in MRL derivation:

[X] 10 for use of a LOAEL
[X] 3.16 for extrapolation from animals to humans because a PBPK model was used
[X] 3.16 for human variability because a PBPK model was used to characterize human toxicokinetic variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? EPA estimated doses using the average of subchronic and chronic reference values for generic body weight and water consumption rates for female B6C3F1 mice.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Johnson et al. (2003)

Reference: Johnson PD, Goldberg SY, Mays MZ, et al. 2003. Threshold of trichloroethylene contamination in maternal drinking waters affecting fetal heart development in the rat. Environ Health Perspect 111(3):289-292.

Experimental design: Groups of pregnant Sprague-Dawley rats (9–13/exposure level) were administered trichloroethylene in the drinking water throughout gestation (GDs 1–22) at concentrations of 0, 0.0025, 0.25, 1.5, or 1,000 ppm. At termination on GD 22, dams and fetuses were examined for gross abnormalities and fetuses were weighed, measured for crown-rump length, and sexed. Fetal hearts and great vessels were examined for gross malformations and prepared for histopathologic evaluations.

Effect noted in study and corresponding doses: Increased incidences of fetuses with cardiac malformations at maternal exposure levels ≥0.25 ppm (estimated maternal doses ≥0.048 mg/kg/day).

Dose and end point used for MRL derivation: Using a benchmark response (BMR) of 1% extra risk that was preferred due to accounting for intralitter effects using a nested model, and pups being the unit of measure, EPA (2011e) calculated a rat lower 95% confidence limit on the benchmark dose ($BMDL_{01}$) of 0.0207 mg/kg/day from the fetal heart malformation incidence data. The highest dose group (1,000-fold higher than next highest) was dropped to improve model fit. The rat $BMDL_{01}$ was 0.0207 mg/kg/day. A PBPK model was used to calculate the idPOD of 0.0142 mg trichloroethylene metabolized by oxidation/kg body weight$^{3/4}$/day. The rat idPOD was converted to a HEC_{99} of 0.0037 ppm for continuous lifetime exposure derived from route-to-route extrapolation and combined interspecies and intraspecies extrapolation using the PBPK model.

[ ] NOAEL [ ] LOAEL [X] HEC_{99}

Uncertainty Factors used in MRL derivation:

[X] 3.16 for extrapolation from animals to humans because a PBPK model was used

[X] 3.16 for human variability because a PBPK model was used to characterize human toxicokinetic variability

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

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: Studies in humans and animals have identified a number of potential targets of trichloroethylene toxicity, including the central nervous system, liver, kidney, immune system, male reproductive system, and the developing fetus. The toxicity of trichloroethylene does not appear to be route-specific; similar effects have been observed following inhalation and oral exposure. The most sensitive toxicity targets appear to be the immune system, the developing fetus, and the kidneys. Immunological effects include alterations in thymus weight and immune function. Decreases in thymus weights were observed in mice exposed to 0.35 mg/kg/day trichloroethylene in drinking water for 30 weeks (Keil et al. 2009) and an impaired response to SRBCs and delayed hypersensitivity were observed in the pups of mice exposed to 0.37 mg/kg/day trichloroethylene in drinking water on GDs 0–21 and for 3 or 8 weeks postpartum (Peden-Adams et al. 2006). At higher doses, other studies have reported increases in splenic lymphocytes (Blossom and Doss 2007) and impaired immune function (Blossom et al. 2008; Sanders et al. 1982). Developmental toxicity studies have demonstrated a number of effects including increases in the occurrence of cardiac malformations in the offspring of rats exposed to 0.048 mg/kg/day trichloroethylene on GDs 0–21 (Johnson et al. 2003) or 0.218 mg/kg/day trichloroethylene in drinking water prior to mating and during gestation (Dawson et al. 1993; Johnson et al. 1998); at higher doses, neurobehavioral effects, decreases in pup body weight, and perinatal mortality have been observed (Manson et al. 1984; NTP 1986; Taylor et al. 1985). Observed renal effects include toxic nephropathy in rats administered via gavage 500 mg/kg trichloroethylene 5 days/week for 2 years (NTP 1988).

EPA employed a PBPK model to calculate an idPOD for plausible internal dose-metrics based on present understanding of the role different trichloroethylene metabolites play in trichloroethylene toxicity and the mode of action for toxicity. The PBPK model was used to estimate interspecies and intraspecies pharmacokinetic variability and resulted in HEC_{99} values for candidate critical effects.

Agency Contact (Chemical Manager): G. Daniel Todd, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Trichloroethylene
CAS Numbers: 79-01-6
Date: June 2019
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 54, 56, 69
Species: Mouse, Rat

Minimal Risk Level: 0.0005 [X] mg/kg/day [ ] ppm

The ATSDR chronic-duration oral MRL of 0.0005 mg/kg/day for trichloroethylene was adopted as the ATSDR intermediate-duration oral MRL (see chronic-duration oral MRL worksheet for more information). The ATSDR chronic-duration oral MRL is based, in part, on results of PBPK modeling exercises that simulated 100 weeks of exposure for humans (EPA 2011e). Sample simulations for a 52-week exposure (within the range of an ATSDR-defined intermediate-duration exposure [15–364 days]) resulted in the same idPOD as the idPOD resulting from simulations for the 100-week exposure.

Agency Contact (Chemical Manager): G. Daniel Todd, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Trichloroethylene
CAS Numbers: 79-01-6
Date: June 2019
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 54, 56, 69
Species: Mouse, Rat

Minimal Risk Level: 0.0005 [X] mg/kg/day [ ] ppm

The chronic-duration oral MRL is based on the results of three critical oral exposure studies that reported immunotoxicity (decreased plaque-forming cell response and increased delayed-type hypersensitivity) in mice (Peden-Adams et al. 2006), decreased thymus weight in female mice (Keil et al. 2009), and fetal heart malformations in rats (Johnson et al. 2003). In the EPA assessment for trichloroethylene (EPA 2011e), independent candidate chronic RfD values were calculated for each of these effects. The Peden-Adams et al. (2006) immunotoxicity LOAEL of 0.37 mg/kg/day was divided by a total uncertainty factor of 1,000 (to account for use of a LOAEL, interspecies extrapolation, and human variability), resulting in a candidate chronic RfD of 0.00037 mg/kg/day. The Keil et al. (2009) thymus weight LOAEL of 0.35 mg/kg/day was used to derive a PBPK model-based human equivalent dose (HED_{99}) of 0.048 mg/kg/day, which was divided by a total uncertainty factor of 100 (to account for use of a LOAEL, interspecies extrapolation, and human variability using a PBPK model), resulting in a candidate chronic RfD of 0.00048 mg/kg/day. The Johnson et al. (2003) fetal heart malformation data were subjected to benchmark dose analysis. The resulting $BMDL_{01}$ (1% extra risk) of 0.0207 mg/kg/day was used to calculate a PBPK model-based HED_{99} of 0.0051 mg/kg/day, which was divided by a total uncertainty factor of 10 (to account for interspecies extrapolation and human variability using a PBPK model). The resulting candidate chronic RfD was 0.00051 mg/kg/day. EPA (2011e) elected to use a chronic RfD value of 0.0005 mg/kg/day and noted that this value was supported by results for multiple effects. ATSDR agreed that this was a reasonable approach. Therefore, the chronic-duration oral MRL is 0.0005 mg/kg/day.

Peden-Adams et al. (2006)

Reference: Peden-Adams MM, Eudaly JG, Heesemann LM, et al. 2006. Developmental immunotoxicity of trichloroethylene (TCE): studies in B6C3F1 mice. J Environ Sci Health A Tox Hazard Subst Environ Eng 41(3):249-271.

Experimental design: Groups of C3H/HeJ male and C57BL/6N female mice (5/sex/group) were administered trichloroethylene in the drinking water at 0, 1.4, or 14 ppm, beginning at pairing (1:1) and continuing for 7 days of mating and throughout gestation (at least for the dams) and lactation. Pups (strain B6C3F1 is produced from the paired parental strains) were evaluated for body length (crown-rump), and timing of eye opening and ear unfolding. At weaning of the pups at 3 weeks of age, 5–7 pups/treatment group, were weighed and sacrificed to assess kidney, liver, thymus, and spleen weights. Trichloroethylene-related effects on the immune system were assessed by measuring splenic lymphocyte proliferation, NK cell activity, SRBC-specific IgM production (PFC response), splenic B220+ cells, and thymic and splenic T-cell immunophenotypes. The remaining pups (4–5 pups/treatment group) were assessed at 8 weeks of age in a manner similar to those assessed at 3 weeks of age, with additional assessments of autoantibodies to dsDNA and delayed type hypersensitivity response (indicated by foot pad swelling following subcutaneous injection of SRBC).

Effect noted in study and corresponding doses: Decreased PFC response was observed in 3- and 8-week-old pups and increased delayed-type sensitivity was noted in 8-week-old pups at 1.4 and 14 ppm trichloroethylene in the drinking water (author-estimated maternal doses of 0.37 and 3.7 mg/kg/day, respectively).

Dose and end point used for MRL derivation: 0.37 mg/kg/day for decreased PFC response and increased delayed-type sensitivity.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

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

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Doses were estimated by the study authors.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Keil et al. (2009)

Reference: Keil DE, Peden-Adams MM, Wallace S, et al. 2009. Assessment of trichloroethylene (TCE) exposure in murine strains genetically-prone and non-prone to develop autoimmune disease. J Environ Sci Health A Tox Hazard Subst Environ Eng 44(5):443-453.

Experimental design: Groups of 9-week-old female B6C3F1 mice (9–10/group) were administered trichloroethylene in the drinking water at 0, 1,400, or 14,000 ppb (1.4 or 14 ppm) in 1% emulphor vehicle for 30 weeks. During the exposure period, serum levels of total IgG and autoantibodies (anti-ssDNA, -dsDNA, and -GA) were monitored. Body weights were recorded 1 day prior to the initiation of trichloroethylene exposure and again at exposure termination. At sacrifice, the spleen, thymus, liver, and kidneys were weighed. Spleen and thymus were processed for assessment of cell counts and activity. Kidneys were processed for histopathologic evaluation; renal pathology was scored by grading glomerular inflammation, crescent formation, and necrosis in histopathology slides.

Effect noted in study and corresponding doses: Decreased thymus weight (30% lower than controls) and increased serum levels of IgG and selected autoantibodies at 1.4 ppm trichloroethylene in the drinking water (EPA-estimated dose of 0.35 mg/kg/day).

Dose and end point used for MRL derivation: A PBPK model was used to calculate the idPOD (idPOD=0.139 mg trichloroethylene metabolized/$kg^{3/4}$/day) from the applied dose LOAEL of 0.35 mg/kg/day. The mouse idPOD was converted to a HED_{99} of 0.048 mg/kg/day for lifetime continuous exposure derived from combined interspecies and intraspecies extrapolation using the PBPK model for trichloroethylene.

[ ] NOAEL [ ] LOAEL [X] HED_{99}

Uncertainty Factors used in MRL derivation:

[X] 10 for use of a LOAEL
[X] 3.16 for extrapolation from animals to humans because a PBPK model was used
[X] 3.16 for human variability because a PBPK model was used to characterize human toxicokinetic variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? EPA estimated doses using the average of subchronic and chronic reference values for generic body weight and water consumption rates for female B6C3F1 mice.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Johnson et al. (2003)

Reference: Johnson PD, Goldberg SY, Mays MZ, et al. 2003. Threshold of trichloroethylene contamination in maternal drinking waters affecting fetal heart development in the rat. Environ Health Perspect 111(3):289-292.

Experimental design: Groups of pregnant Sprague-Dawley rats (9–13/exposure level) were administered trichloroethylene in the drinking water throughout gestation (GDs 1–22) at concentrations of 0, 0.0025, 0.25, 1.5, or 1,000 ppm. At termination on GD 22, dams and fetuses were examined for gross abnormalities and fetuses were weighed, measured for crown-rump length, and sexed. Fetal hearts and great vessels were examined for gross malformations and prepared for histopathologic evaluations.

Effect noted in study and corresponding doses: Increased incidences of fetuses with cardiac malformations at maternal exposure levels ≥0.25 ppm (estimated maternal doses ≥0.048 mg/kg/day).

Dose and end point used for MRL derivation: Using a BMR of 1% extra risk that was preferred due to accounting for intralitter effects using a nested model, and pups being the unit of measure, EPA (2011e) calculated a rat $BMDL_{01}$ of 0.0207 mg/kg/day from the fetal heart malformation incidence data. The highest dose group (1,000-fold higher than next highest) was dropped to improve model fit. The rat $BMDL_{01}$ was 0.0207 mg/kg/day. A PBPK model was used to calculate the idPOD of 0.0142 mg trichloroethylene metabolized by oxidation/kg body weight$^{3/4}$/day. The rat idPOD was converted to a HED_{99} of 0.0051 mg/kg/day for continuous lifetime exposure derived from combined interspecies and intraspecies extrapolation using the PBPK model for trichloroethylene.

[ ] NOAEL [ ] LOAEL [X] HED_{99}

Uncertainty Factors used in MRL derivation:

[X] 3.16 for extrapolation from animals to humans because a PBPK model was used
[X] 3.16 for human variability because a PBPK model was used to characterize human toxicokinetic variation

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

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: Studies in humans and animals have identified a number of potential targets of trichloroethylene toxicity including the central nervous system, liver, kidney, immune system, male reproductive system, and the developing fetus. The toxicity of trichloroethylene does not appear to be route-specific; similar effects have been observed following inhalation and oral exposure. The most sensitive toxicity targets appear to be the immune system, the developing fetus, and the kidneys. Immunological effects include alterations in thymus weight and immune function. Decreases in thymus weights were observed in mice exposed to 0.35 mg/kg/day trichloroethylene in drinking water for 30 weeks (Keil et al. 2009) and an impaired response to SRBCs and delayed hypersensitivity were observed in the pups of mice exposed to 0.37 mg/kg/day trichloroethylene in drinking water on GDs 0–21 and for 3 or 8 weeks postpartum (Peden-Adams et al. 2006). At higher doses, other studies have reported increases in splenic lymphocytes (Blossom and Doss 2007) and impaired immune function (Blossom et al. 2008; Sanders et al. 1982). Developmental toxicity studies have demonstrated a number of effects including increases in the occurrence of cardiac malformations in the offspring of rats exposed to 0.048 mg/kg/day trichloroethylene on GDs 0–21 (Johnson et al. 2003) or 0.218 mg/kg/day trichloroethylene in drinking water prior to mating and during gestation (Dawson et al. 1993; Johnson et al. 1998); at higher doses, neurobehavioral effects, decreases in pup body weight, and perinatal mortality have been observed (Manson et al. 1984; NTP 1986; Taylor et al. 1985). Observed renal effects include toxic nephropathy in rats administered via gavage 500 mg/kg trichloroethylene 5 days/week for 2 years (NTP 1988).

EPA employed a PBPK model to calculate an idPOD for plausible internal dose-metrics based on present understanding of the role different trichloroethylene metabolites play in trichloroethylene toxicity and the mode of action for toxicity. The PBPK model was used to estimate interspecies and intraspecies pharmacokinetic variability and resulted in HED_{99} values for candidate critical effects.

Agency Contact (Chemical Manager): G. Daniel Todd, Ph.D.

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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 hazardous substance 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 include 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 adverse 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 an adverse 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

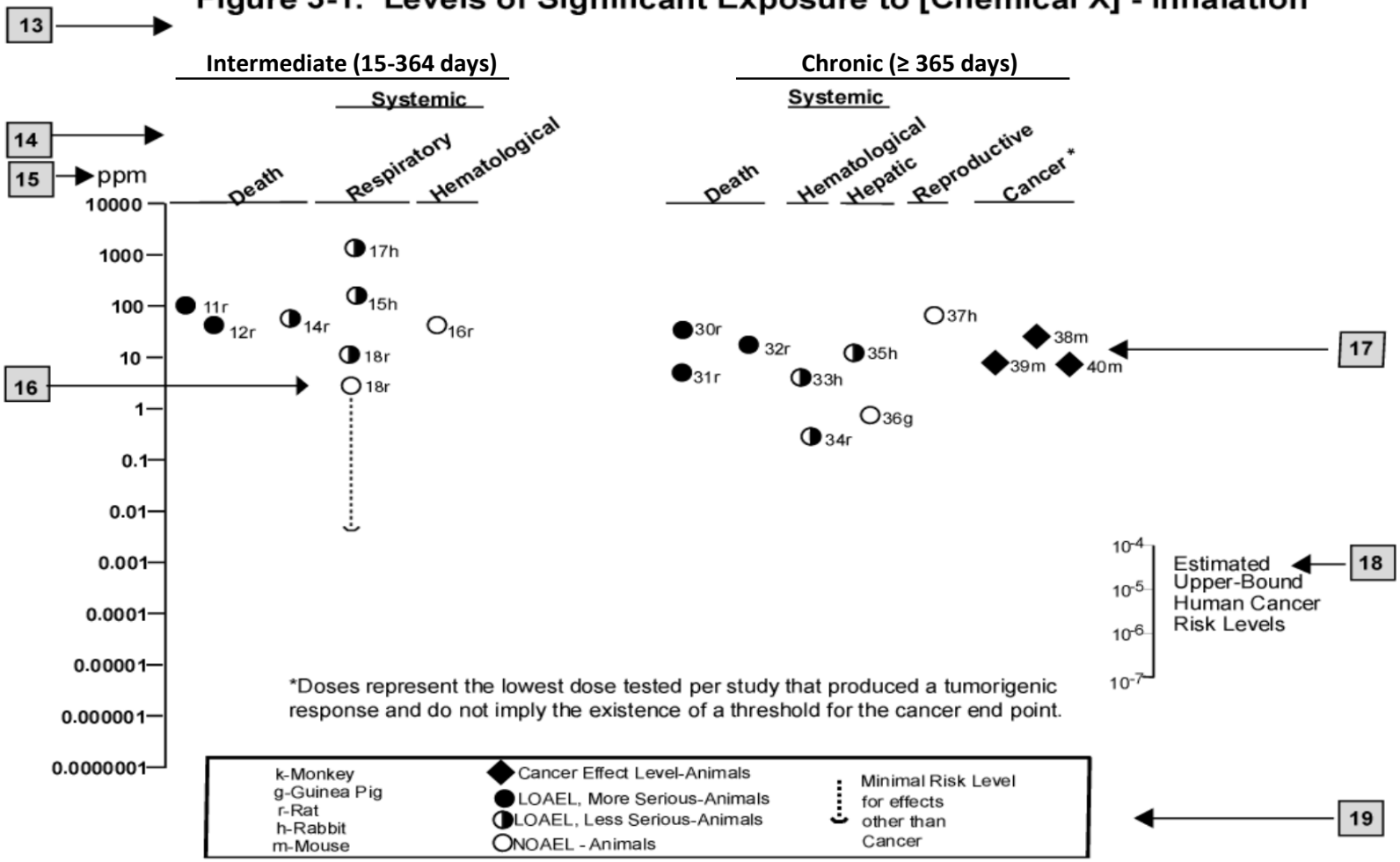
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

	Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) 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 5×10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
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
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/IMDG	Department of Transportation/United Nations/North America/Intergovernmental Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 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
mt	metric ton
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
PEL-C	permissible exposure limit-ceiling value
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
REL-C	recommended exposure level-ceiling value
RfC	reference concentration (inhalation)
RfD	reference dose (oral)
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 (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
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
TLV-C	threshold limit value-ceiling 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