TOXICOLOGICAL PROFILE FOR TRICHLOROETHYLENE

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

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DISCLAIMER

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UPDATE STATEMENT

An update Toxicological Profile for Trichloroethylene was released in April 1993. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary, but no less than once every three years. For information regarding the update status of previously released profiles, contact ATSDR at:

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FOREWORD

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

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

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

Each profile includes the following:

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

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

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

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

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

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

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The Chemical Manager and Authors acknowledge the contribution of Dr. Ted W. Simon, U.S. EPA, in applying physiologically-based pharmacokinetic modeling to the development of minimal risk levels for trichloroethylene.

THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Green Border Review. Green Border review assures consistency with ATSDR policy.

2. 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.

3. 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.

PEER REVIEW

A peer review panel was assembled for trichloroethylene. The panel consisted of the following members:

1. Herbert Cornish, Ph.D., Private Consultant, Ypsilanti, MI
2. James Klaunig, Ph.D., Indiana University School of Medicine, Indianapolis, IN
3. Norbert Page, Ph.D., Private Consultant, Gaithersburg, MD

These experts collectively 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.

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

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

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about trichloroethylene and the effects of exposure.

The Environmental Protection Agency (EPA) has identified 1,428 hazardous waste sites as the most serious in the nation. These sites make up the National Priorities List (NPL) and are targeted for long-term federal clean-up. Trichloroethylene has been found in at least 861 NPL sites. However, it's unknown how many NPL sites have been evaluated for this substance. As EPA looks at more sites, the sites with trichloroethylene may increase. This is important because exposure to this substance may harm you and because these sites may be sources of exposure.

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

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

1.1 WHAT IS TRICHLOROETHYLENE?

Trichloroethylene is also known as Triclene and Vitran and by other trade names in industry. It is a nonflammable, colorless liquid at room temperature with a somewhat sweet odor and a sweet, burning taste. Trichloroethylene is now mainly used as a solvent to remove grease from metal parts. It is also used as a solvent in other ways and is used to make other chemicals. Trichloroethylene can also be found in some household products, including typewriter correction fluid, paint removers, adhesives, and spot removers. Most people can begin to smell trichloroethylene in air when there are around 100 parts of trichloroethylene per million parts of air (ppm). Further information on the physical and chemical properties of trichloroethylene can be found in Chapter 3, and further information on its production and use can be found in Chapter 4.

1.2 WHAT HAPPENS TO TRICHLOROETHYLENE WHEN IT ENTERS THE ENVIRONMENT?

By far, the biggest source of trichloroethylene in the environment is evaporation from factories that use it to remove grease from metals. It can also enter the air and water when it is disposed of at chemical waste sites. It evaporates easily but can stay in the soil and in groundwater. Once it is in the air, about half will be broken down within a week. When trichloroethylene is broken down in the air, phosgene, a lung irritant, can be formed. Trichloroethylene can break down under high heat and alkaline conditions to form dichloroacetylene and phosgene. In the body, trichloroethylene may break down into dichloroacetic acid (DCA), trichloroacetic acid (TCA), chloral hydrate, and 2-chloroacetaldehyde. These products have been shown to be toxic to animals and are probably toxic to humans. Once trichloroethylene is in water, much will evaporate into the air; again, about half will break down within a week. It will take days to weeks to break down in surface water. In groundwater the breakdown is much slower because of the much slower evaporation rate. Very little trichloroethylene breaks down in the soil, and it can pass through the soil into underground water. It is found in some foods. The trichloroethylene found in foods is believed to come from contamination of the water used in food processing, or from food processing equipment cleaned with trichloroethylene. It does not build up in fish, but low levels have been found in them. It is not likely to build up in your body. For more information on trichloroethylene in the environment, see Chapters 4 and 5.

1.3 HOW MIGHT I BE EXPOSED TO TRICHLOROETHYLENE?

Trichloroethylene is found in the outdoor air at levels far less than 1 ppm. When measured several years ago, some of the water supplies in the United States were found to have tuichloroethylene. The most recent monitoring study found average levels in surface water ranging from 0.0001 to 0.001 ppm of water and an average level of 0.007 ppm in groundwater. About 400,000 workers are routinely exposed to trichloroethylene in the United States. The chemical can also get into the air or water in many ways, for example, at waste treatment facilities; by evaporation from paints, glues, and other products; or by release from factories where it is made. Another way you may be exposed is by breathing the air around factories that use the chemical. People living near hazardous waste sites may be exposed to it in the air or in

their drinking water, or in the water used for bathing or cooking. Products that may contain trichloroethylene are some types of typewriter correction fluids, paints and paint removers, glues, spot removers, rug cleaning fluids, and metal cleaners. For more information on exposure to trichloroethylene, see Chapter 5.

1.4 HOW CAN TRICHLOROETHYLENE ENTER AND LEAVE MY BODY?

Trichloroethylene enters your body when you breathe air or drink water containing it. It can also enter your body if you get it on your skin. You could be exposed to contaminated water or air if you live near or work in a factory that uses trichloroethylene or if you live near a waste disposal site that contains trichloroethylene. If you breathe the chemical, about half the amount you breathe in will get into your bloodstream and organs. You will exhale the rest. If you drink trichloroethylene, most of it will be absorbed into your blood. If trichloroethylene comes in contact with your skin, some of it can enter your body, although not as easily as when you breathe or swallow it.

Once in your blood, your liver changes much of the trichloroethylene into other chemicals. The majority of these breakdown products leave your body in the urine within a day. You will also quickly breathe out much of the trichloroethylene that is in your bloodstream. Some of the trichloroethylene or its breakdown products can be stored in body fat for a brief period, and thus may build up in your body if exposure continues. For more information on trichloroethylene in your body, see Chapter 2.

1.5 HOW CAN TRICHLOROETHYLENE AFFECT MY HEALTH?

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

One way to see if a chemical will hurt people is to learn how the chemical is absorbed, used, and released by the body; for some chemicals, animal testing may be necessary. Animal testing may also be used to identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method to get information needed to make wise decisions to protect public health. Scientists have the responsibility to treat research animals with care and compassion. Laws today protect the welfare of research animals, and scientists must comply with strict animal care guidelines.

Trichloroethylene was once used as an anesthetic for surgery. People who are exposed to large amounts of trichloroethylene can become dizzy or sleepy and may become unconscious at very high levels. Death may occur from inhalation of large amounts. Many people have jobs where they work with trichloroethylene and can breathe it or get it on their skin. Some people who get concentrated solutions of trichloroethylene on their skin develop rashes. People who breathe moderate levels of trichloroethylene may have headaches or dizziness. It is possible that some people who breathe high levels of trichloroethylene may develop damage to some of the nerves in the face. People have reported health effects when exposed to the level of trichloroethylene at which its odor is noticeable. Effects have also occurred at much higher levels. The effects reported at high levels include liver and kidney damage and changes in heart beat. The levels at which these effects occur in humans are not well characterized. Animals that were exposed to moderate levels of trichloroetbylene had enlarged livers, and high-level exposure caused liver and kidney damage.

It is uncertain whether people who breathe air or drink water containing trichloroethylene are at higher risk of cancer, or of having reproductive effects. More and more studies suggest that more birth defects may occur when mothers drink water containing trichloroethylene. People who used water for several years from two wells that had high levels of trichloroethylene may have had a higher incidence of childhood leukemia than other people, but these findings are not conclusive. In another study of trichloroethylene exposure from well water, increased numbers of children

were reported to be born with heart defects, which is supported by data from some animal studies showing developmental effects of trichloroethylene on the heart. However, other chemicals were also in the water from this well and may have contributed to these effects. One study reported a higher number of children with a rare defect in the respiratory system and eye defects. Another study reported that the risk for neural tube defects and oral cleft palates were higher among mothers with trichloroethylene in their water during pregnancy. Children listed in the National Exposure Subregistry of persons exposed to trichloroethylene were reported to have higher rates of hearing and speech impairment. There are many questions regarding these reports. There were small numbers of children with defects and trichloroethylene levels at which the effects occurred were not defined well. Thus, it is not possible to make firm conclusions about the exact effects of trichloroethylene from these studies, and more studies need to be done.

We do not have any clear evidence that trichloroethylene alone in drinking water can cause leukemia or any other type of cancer in humans. As part of the National Exposure Subregistry, the Agency for Toxic Substances and Disease Registry (ATSDR) compiled data on 4,280 residents of three states (Michigan, Illinois, and Indiana) who had environmental exposure to trichloroethylene. It found no definitive evidence for an excess of cancers from trichloroethylene exposure. An increase of respiratory cancer was noted in older men, but this effect was thought to result from smoking rather than trichloroethylene exposure. A study in New Jersey found an association between leukemia in women and exposure to trichloroethylene in the drinking water. A study in Massachusetts found that exposure was associated with leukemia in children. In studies with people, there are many factors that are not fully understood. More studies need to be done to establish the relationship between exposure to trichloroethylene and cancer.

In studies using high doses of trichloroethylene in rats and mice, tumors in the lungs, liver, and testes were found, providing some evidence that high doses of trichloroethylene can cause cancer in experimental animals. Based on the limited data in humans regarding trichloroethylene exposure and cancer, and evidence that high doses of trichloroethylene can cause cancer in animals, the International Agency for Research on Cancer (IARC) has determined that trichloroethylene is probably carcinogenic to humans. Trichloroethylene has been nominated for listing in the National Toxicology Program (NTP) 9th Report on Carcinogens. Evaluation of this substance by the NTP review committee is ongoing. For more information on how trichloroethylene can affect your health see Chapter 2.

1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO TRICHLOROETHYLENE?

There are some tests that can show if you have been recently exposed to trichloroethylene since this chemical can be measured in your breath. Also, a doctor can have trichloroethylene or a number of breakdown products of trichloroethylene measured in your urine or blood. None of these tests, however, is routinely available at your doctor's office. If the measurements are done soon after the exposure, the breath levels can indicate whether you have been exposed to a large amount of trichloroethylene or only a small amount. Urine and blood tests can also show if you have been exposed to large amounts of this chemical. Because one of the breakdown products leaves your body very slowly, it can be measured in the urine for up to about 1 week after trichloroethylene exposure. However, exposure to other similar chemicals can produce the same breakdown products in your urine and blood. Therefore, these methods cannot determine for sure whether you have been exposed to trichloroethylene. For more information on medical tests, see Chapters 2 and 6.

1.7 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 cannot be enforced 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 in not-to-exceed levels in air, water, soil, or food that are usually based on levels that affect animals, then they are adjusted to help protect people. Sometimes these not-to-exceed levels differ among federal organizations because of

different exposure times (an g-hour workday or a 24-hour day), the use of different animal studies, or other factors.

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

EPA has set a drinking water standard of 5 parts of trichloroethylene per one billion parts of water (ppb). One ppb is 1,000 times less than 1 ppm. This standard became effective on January 9, 1989, and applies to community water systems and those that serve the same 25 or more persons for at least 6 months. EPA requires industries to report spills of 1,000 pounds or more of trichloroethylene. It has been proposed that this level be reduced to 100 pounds.

Trichloroethylene levels in the workplace are regulated by the Occupational Safety and Health Administration (OSHA). The occupational exposure limit for an 8-hour workday, 40-hour workweek, is an average concentration of 100 ppm in air. The 15-minute average exposure in air that should not be exceeded at any time during a workday is 300 ppm. The OSHA standards are based on preventing central nervous system effects after trichloroethylene exposure. For more information, see Chapter 7.

1.8 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department or:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE, Mailstop E-29
Atlanta, Georgia 30333

*Information line and technical assistance

Phone: (404) 639-6000
Fax: (404) 639-6315 or 6324

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

*To order toxicolopical profiles. contact:

National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161
Phone (800) 553-6847 or (703) 487-4650

2. HEALTH EFFECTS

2.1 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.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

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

used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between “less serious” and “serious” effects. The distinction between “less serious” effects and “serious” effects is considered to be important because it helps 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 or exposure levels below which no adverse effects have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or h4RLs) 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 2-l and 2-2 and Figures 2-1 and 2-2.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or 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 noncancer health effects only and do not reflect a consideration of carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

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

repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

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

2.2.1 Inhalation Exposure

2.2.1.1 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, often during its use in degreasing operations (Ford et al. 1995; James 1963; Kleinfeld and Tabershaw 1954; McCarthy and Jones 1983; Smith 1966) or dry-cleaning operations (Bell 1951). These studies usually attributed death to ventricular fibrillation or central nervous system depression, since gross post-mortem abnormalities were not apparent. 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 intentional inhalation of concentrated fumes from trichloroethylene-containing typewriter correction fluid (Troutman 1988) and cleaning fluids (Clear-field 1970). 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.

Animal experimentation has revealed inhaled concentrations that result in death following acute, intermediate, and chronic exposure. An LC_{50} value for acute exposure in rats was reported as 12,500 ppm for a 4-hour exposure (Siegel et al. 197i). 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 2-l and plotted in Figure 2- 1.

2.2.1.2 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 2- 1 and plotted in Figure 2- 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.

Morphology of lung cells and P-450 activity in the lungs has been studied in rats and mice exposed to trichloroethylene. A 30minute inhalation exposure to 500 ppm resulted in vacuole formation and endoplasmic reticulum dilation specifically in the nonciliated epithelial cells (Clara cells) of the bronchial tree (Villas&i 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 P-450 enzyme 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).

TABLE 2-1. Levels of Significant Exposure to Trichloroethylene - Inhalation

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (ppm)		LOAEL (effect) Less serious (ppm)		LOAEL (effect) Serious (ppm)		Reference
	ACUTE EXPOSURE									
	Death									
1	Rat (Sprague-Dawley)	4 hr						12500 M	(LC_{50})	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

TABLE 2-1. Levels of Significant Exposure to Trichloroethylene - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)		LOAEL (effect) Serious (ppm)	Reference
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
7	Rat (Alpk: APfSD)	6 hr	Resp		500 F	(reduction of aldrin epoxidase and cytochrome C reductase activity)		Odum et al. 1992
8	Mouse (CD-1)	6 hr	Resp	20 F	100 F	(vacuolization of Clara cells, reduction of P-450 activity)		Odum et al. 1992
9	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
10	Mouse (B6C3F1)	30 min	Resp		500 M	(vacuolization and dilation of endoplasmic reticulum in Clara cells)		Villaschi et al. 1991

TABLE 2-1. Levels of Significant Exposure to Trichloroethylene - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)		Serious (ppm)		Reference
11	Dog (Beagle)	10 min	Cardio	5000 M			10000 M	(7/12 ventricular fibrillation after epinephrine challenge, 1/12 cardiac arrest)	Reinhardt et al. 1973
	Immunological/Lymphoreticular								
12	Mouse (CD-1)	3 hr		5 F	10 F	(increased susceptibility to *Streptococcus zooepidemicus*)			Aranyi et al. 1986
	Neurological								
13	Human	2.5 hr		300 M					Ettema et al. 1975
14	Human	~1 hr					3000 M	(unconsciousness)	Longley and Jones 1963
15	Human	5 d 7 hr/d			200[b]	(headache, fatigue, drowsiness)			Stewart et al. 1970
16	Human	2 hr		300 M			1000 M	(decreased depth perception and motor skills)	Vernon and Ferguson 1969
17	Human	2.5 hr		200 M					Windemuller and Ettema 1978

TABLE 2-1. Levels of Significant Exposure to Trichloroethylene - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)		LOAEL (effect) Serious (ppm)		Reference
18	Rat (Wistar)	8 hr			3000	(lethargy)	4800	(anesthesia)	Adams et al. 1951
19	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
20	Rat (Long-Evans)	5 d 6 hr/d		2000 M			4000 M	(postexposure mid-frequency hearing loss, sedation)	Crofton and Zhao 1993
21	Rat (CFE)	10 d 5 d/wk 4 hr/d		1568 F			4380 F	(ataxia)	Goldberg et al. 1964b
22	Rat (NS)	6 hr		400 M	800 M	(impaired swimming performance both with and without a load)			Grandjean 1963
23	Rat (Wistar)	4 hr			250 M	(decreased shock avoidance and Skinner box lever press)			Kishi et al. 1993
24	Rat (pigmented	1 hr			2754	(impaired oculomotor control)			Niklasson et al. 1993

TABLE 2-1. Levels of Significant Exposure to Trichloroethylene - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
25	Rat (Sprague-Dawley)	4 d 6 hr/d			200 M (decreased brain RNA, hyperactivity)		Savolainen et al. 1977
	Reproductive						
26	Mouse (C57Bl/ 6J)	5 d 6 hr/d		500 M			Allen et al. 1994
27	Mouse (CD-1)	5 d 7 hr/d			100 M (6% increase in abnormal sperm morphology)		Beliles et al. 1980
28	Mouse (C57BL/ 6N)	5 d 4 hr/d		200 M	2000 M (1% increase in abnormal sperm morphology)		Land et al. 1981
	Developmental						
29	Rat (Sprague-Dawley)	Gd 0-18 5 d/wk 7 hr/d		500			Beliles et al. 1980; Hardin et al. 1981
30	Rat (Long-Evans)	Gd 0-20 7 d/wk 6 hr/d			1800 (decreased fetal weight, incomplete skeletal ossification)		Dorfmueller et al. 1979
31	Rat (Sprague-Dawley)	Gd 6-15 7 hr/d		300			Schwetz et al. 1975

TABLE 2-1. Levels of Significant Exposure to Trichloroethylene - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (ppm)		LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
32	Mouse (Swiss-Webster)	Gd 6-15 7 hr/d		300				Schwetz et al. 1975
	INTERMEDIATE EXPOSURE							
	Systemic							
33	Monkey (Rhesus)	6 mo 5 d/wk 7 hr/d	Hepatic	400	M			Adams et al. 1951
			Renal	400	M			
			Bd Wt	400	M			
34	Rat (Wistar)	6 mo 5 d/wk 7 hr/d	Hemato	400				Adams et al. 1951
			Hepatic	400				
			Renal	400				
			Bd Wt	400				
35	Rat (Wistar)	10 wk 5 d/wk 8 hr/d	Hepatic	2000				Laib et al. 1979

TABLE 2-1. Levels of Significant Exposure to Trichloroethylene - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
36	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			
37	Rat (Sprague-Dawley)	90 d 24 hr/d	Resp	35			Prendergast et al. 1967
			Cardio	35			
			Hemato	35			
			Hepatic	35			
			Renal	35			
38	Mouse (NMRI)	30 d 24 hr/d	Hepatic	37 M	75 M	(increased BuChE activity, liver weight)	Kjellstrand et al. 1983a
				150 F	300 F	(increased BuChE activity, liver weight)	
			Bd Wt	75 M	150 M	(body weights 10% lower than controls)	
				150 F	300 F	(body weights 16% lower than controls)	

TABLE 2-1. Levels of Significant Exposure to Trichloroethylene - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)		LOAEL (effect) Serious (ppm)		Reference
39	Rabbit (NS)	6 mo 5 d/wk 7 hr/d	Hepatic	400					Adams et al. 1951
			Renal	400					
			Bd Wt	400					
40	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)			
	Neurological								
41	Rat (Fischer-344)	13 wk 5 d/wk 6 h/d		250	800	(altered amplitude of flash-evoked potentials)			Albee et al. 1993
42	Rat (JCL-Wistar)	6 wk 5 d/wk 8 hr/d			50 cM	(decreased wakefulness during exposure, decreased postexposure sleeping heart rate)	100 M	(decreased postexposure wakefulness, decreased time-averaged postexposure heart rate)	Arito et al. 1994a
43	Rat (NS)	44 wk 5 d/wk 8 hr/d			400 M	(decreased swimming speed)			Battig and Grandjean 1963

TABLE 2-1. Levels of Significant Exposure to Trichloroethylene - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
44	Rat (CFE)	30 d 5 d/wk 4 hr/d			125 M (decreased shock avoidance)		Goldberg et al. 1964a
45	Rat (Wistar)	3 wk 5 d/wk 18 hr/d			1500 (reduced acoustic startle response)		Jaspers et al. 1993
46	Rat (Wistar)	18 wk 5 d/wk 16 hr/d		500 M	1000 M (increased latency in visual discrimination task)		Kulig 1987
47	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
48	Rat (Fischer-344)	3 wk 6 d/wk 12 hr/d			2000 M (depressed amplitude of auditory-evoked potentials)		Rebert et al. 1991
49	Rat (Wistar)	5 wk 5 d/wk 6 hr/d			100 M (reduced social behavior: exploration, escape, submission)		Silverman and Williams 1975
50	Rabbit (New Zealand)	12 wk 4 d/wk 4 hr/d			350 (altered amplitude of visual-evoked potentials)		Blain et al. 1992

TABLE 2-1. Levels of Significant Exposure to Trichloroethylene - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
51	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
52	Gerbil (Mongolian)	3 mo 24 hr/d			60 (astroglial hypertrophy)		Haglid et al. 1981
	CHRONIC EXPOSURE						
	Systemic						
53	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			
			Derm	600			
			Ocular	600			
			Bd Wt	600			
	Cancer						
54	Rat (Sprague-Dawley)	104 wk 5 d/wk 7 hr/d				100 M (CEL: Leydig cell tumors)	Maltoni et al. 1986

TABLE 2-1. Levels of Significant Exposure to Trichloroethylene - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)		Reference
55	Mouse (ICR)	104 wk 5 d/wk 7 hr/d				150 F	(CEL: lung adenomas and adenocarcinomas)	Fukuda et al. 1983
56	Mouse (NMRI)	18 mo 5 d/wk 6 hr/d				100 F	(CEL: increased lymphomas)	Henschler et al. 1980
57	Mouse (B6C3F1)	78 wk 5 d/wk 7 hr/d				600 F	(CEL: pulmonary tumors)	Maltoni et al. 1986
58	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 2-1. Differences in levels of health effects and cancer effects between males and females are not indicated in Figure 2-1. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

[b]Used to derive an acute-duration inhalation Minimal Risk Level (MRL) of 2 ppm for trichloroethylene; 200 ppm duration-adjusted (7/24 hr) to 58.3 ppm, divided by an uncertainty factor of 30 (3 for use of a minimal LOAEL, 10 for human variability) = 1.9 ppm, rounded to 2 ppm.

[c]Used to derived an intermediate-duration inhalation Minimal Risk Level (MRL) of 0.1 ppm for trichloroethylene; 50 ppm adjusted for duration (5/7 days x 8 hr/d) and species-specific ratio of daily inhalation volume (m^3/day)/body weight(kg) ratio for rat (0.23/2.17) to human (20/70) to 44.2 ppm, divided by an uncertainty factor of 300 (10 for using a LOAEL, 3 for extrapolation from animals to humans, and 10 for human variability) = 0.147 ppm, rounded to 0.1 ppm.

Bd Wt = body weight; BuChE = butyrylcholinesterase; Cardio = cardiovascular; CEL = cancer effect level; contin = continuous; d = day(s); Derm = dermal; Endocr = endocrine; F = female; Gastro = gastrointestinal; Gd = gestation day(s); Gn pig = guinea pig; Hemato = hematological; hr = hour(s); LC_{50} = 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; Resp = respiratory; wk = week(s)

Figure 2-1. Levels of Significant Exposure to Trichloroethylene - Inhalation

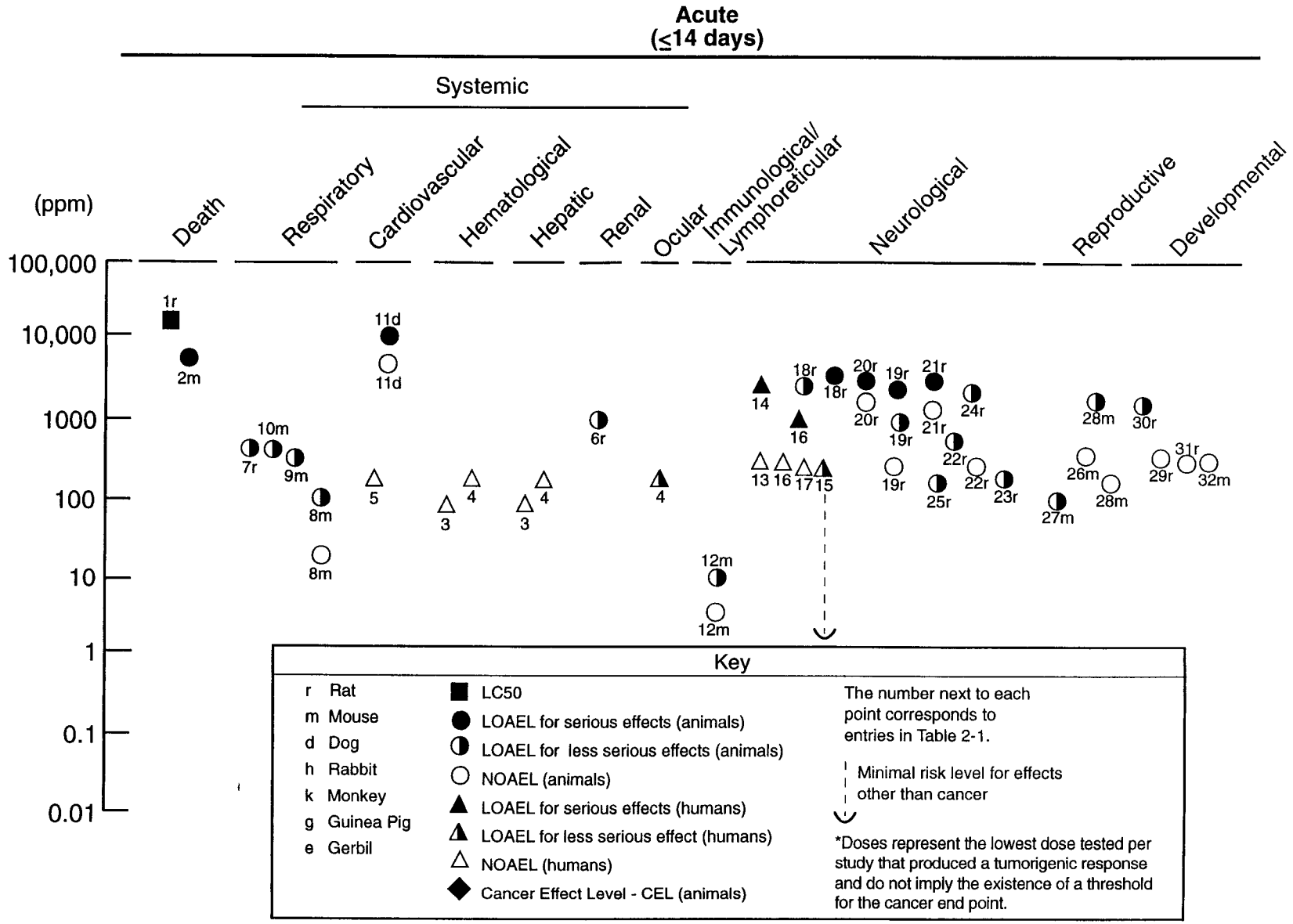


Figure 2-1. Levels of Significant Exposure to Trichloroethylene - Inhalation (continued)

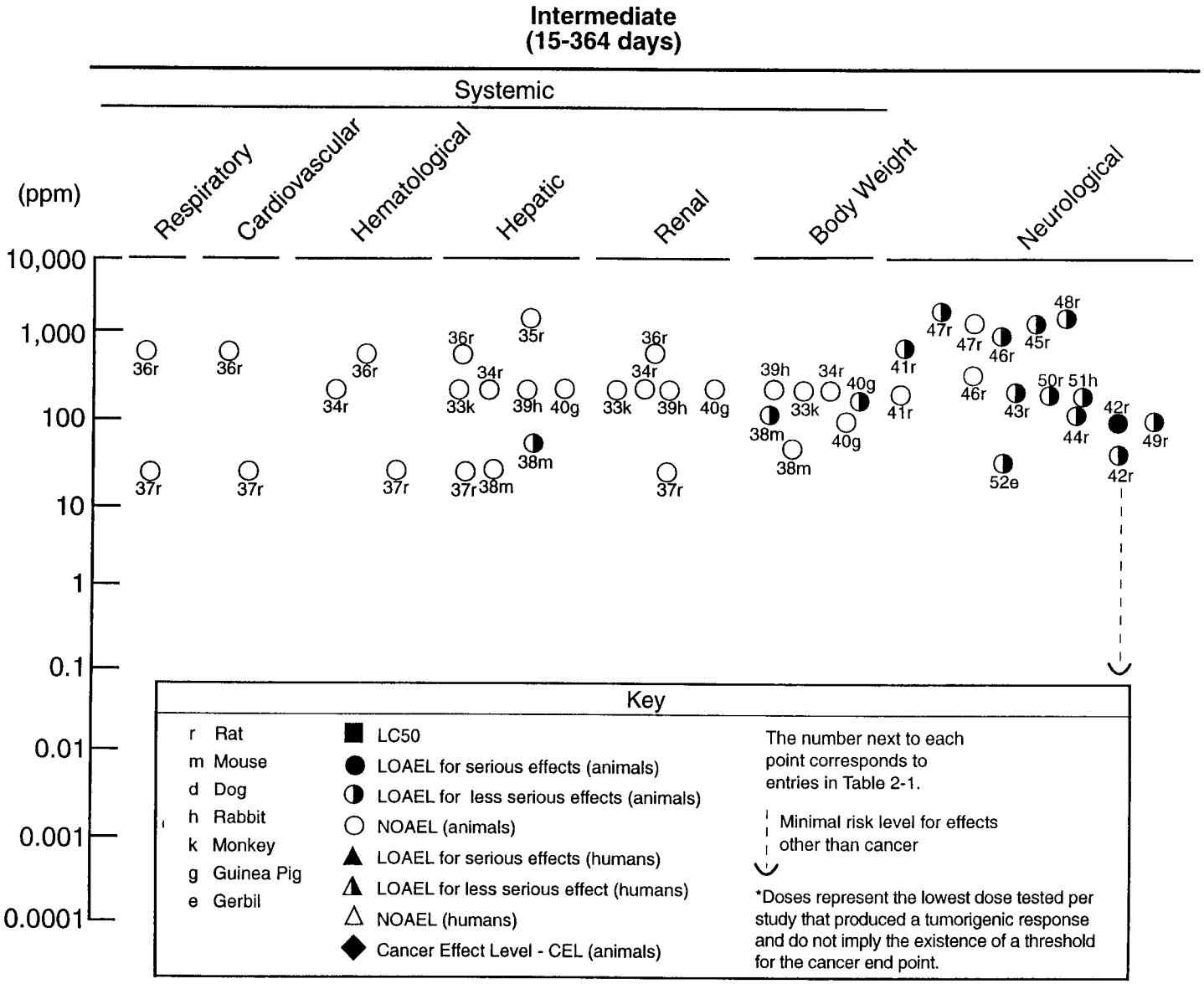
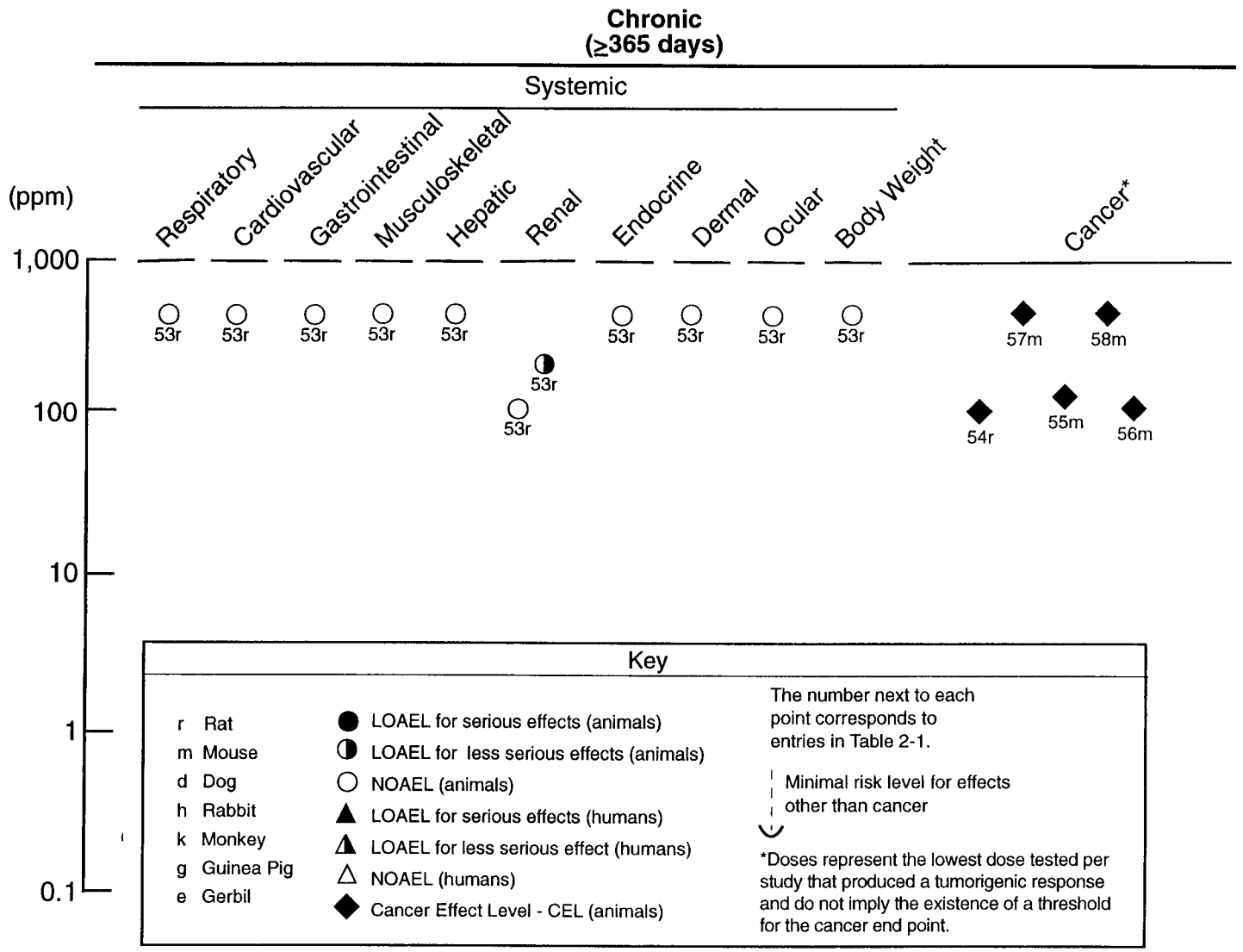


Figure 2-1. Levels of Significant Exposure to Trichloroethylene - Inhalation (continued)



Cardiovascular Effects. Exposure of 15 male volunteers to 200 ppm trichloroethylene for 2.5 hours had no effect on heart rate or sinus arrhythmia (Windemuller and Ettema 1978). Electrocardiograms of workers exposed to trichloroethylene in the range of 38-172 ppm for periods ranging from less than 1 year to more than 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). Hypertension, enlarged heart, and arrhythmia were seen in some workers (number, sex, and exposure period unspecified) accidentally exposed to trichloroethylene at a level that was unspecified but at least 15 ppm (Sidorin et al. 1992). Previous chronic exposure to trichloroethylene from using shoemaker's glue in an unventilated shop was implicated in a case of cardiac arrest and subsequent arrhythmia (Wemisch et al. 1991). 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 Mahrick 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 an acute 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 95 ppm trichloroethylene 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 less than 1 year to more than 5 years (El Ghawabi et al. 1973).

Various minor hematological effects have been noted in animals. Rats exposed to 50-800 ppm of trichloro-ethylene 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 400 ppm (Adams et al. 1951) or 55 ppm (Kimmerle and Eben 1973a).

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after inhalation exposure to trichloroethylene. Trichloroethylene exposure can result in nervous system effects that result in secondary effects on muscle strength, especially in the face (Leandri et al. 1995). See Section 2.2.1.4 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 of trichloroethylene exposure that support the liver as an end point of trichloroethylene toxicity are described below. There is one report that occupational exposure to high concentrations of trichloroethylene resulted in death, with acute massive liver necrosis 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 succumbed to trichloroethylene exposure following 10 years of intentional overexposure.

A review of older case studies includes some 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). A more recent report (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 (SGOT) which returned to normal within 2 or 3 days. One patient had a doubling of the SGOT 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 data available 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 (Capellini and Grisler 1958; 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). Case studies 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). Case studies of 289 British workers, who had neurological effects from trichloroethylene, revealed no cases with a clear diagnosis of hepatotoxicity (McCarthy and Jones 1983). 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 (Schuttmann 1970). Liver function tests were normal in human 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). The available evidence suggests that hepatic damage may occur in some people following chronic exposure to relatively high levels in the workplace, but the available reports are conflicting.

Inhalation of trichloroethylene for acute or intermediate periods can cause liver enlargement in laboratory animals. Usually this effect is 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 enlarged and vacuolated hepatocytes. Liver weight, liver histology, and serum BuChE activity returned to normal 4 months later, indicating reversibility of the hepatic effects. Male mice were more sensitive to this effect 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), 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). Relative liver weight was increased 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. Pathological examinations were not conducted in this study.

Other investigators either found no microscopic lesions in the liver of animals exposed to trichloroethylene or did not perform histopathology. 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 noted (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 a day, 5 days per week for 10 weeks (Laib et al. 1979). Histopathological changes were also not observed in the livers of rats exposed to 300 ppm trichloroethylene 7 hours per day, 5 days per week for 104 weeks (Maltoni et al. 1988).

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 exposed 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 (Cleat-field 1970). Slight renal effects indicated by changes in urinary proteins (Brogren et al. 1986) and N-acetyl-P-D-glucosaminidase (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 the tubules.

Exposure of rats to extremely high levels (1,000 ppm or higher) for periods of less than 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). Increased kidney weight has been found in rats, mice, and gerbils exposed for intermediate periods (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. Other investigators also found increases in kidney weight following intermediate-duration exposure but no histopathological changes in squirrel monkeys or dogs (Prendergast et al. 1967); in rhesus monkeys (Adams et al. 1951); or in rats, guinea pigs, or rabbits

(Adams et al. 1951; Prendergast et al. 1967). Since the histological observations were unremarkable, and other functional tests were not performed, the levels at which only kidney weight was altered were considered to be NOAELs. Male rats, but not females, that were exposed to 300 ppm trichloroethylene in a chronic study showed renal tubular meganucleocytosis (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 2.2.1.8.

Endocrine Effects. No studies were located regarding endocrine effects in humans after inhalation exposure to trichloroethylene.

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).

Dermal Effects. Humans that 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. Skin irritation and rashes have resulted from occupational exposure to trichloroethylene (Bauer and Rabens 1974; El Ghawabi et al. 1973). The dermal effects 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.

Stevens-Johnson syndrome, a severe erythema, 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). The study authors suggested that the erythema was caused by a hypersensitivity reaction to trichloroethylene. An exfoliative dermatitis (Goh and Ng 1988) and scleroderma (Czirjak et al. 1993), also thought to have an immune component, have been reported in persons occupationally exposed to trichloroethylene.

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 that 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.

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).

Body weights were lower than controls (18% males, 16% females) in mice exposed continuously to 300 ppm trichloroethylene for 30 days (Kjellstrand et al. 1983a). At 150 ppm, body weights of male mice were 10% lower than controls, while no effects on body weight were observed in female mice. Male guinea pigs also appear to be more sensitive to effects on body weight compared to females. Body weights were 18% lower than controls in male guinea pigs exposed to 200 ppm trichloroethylene 7 hours per day, 5 days per week for 6 months (Adams et al. 1951). No effects on body weight were noted in female guinea pigs exposed to 400 ppm. Body weight was not affected in rhesus monkeys, rats, or rabbits exposed to 400 ppm 7 hours per day, 5 days per week for 6 months (Adams et al. 1951); in rats exposed to 700 ppm 8 hours per day, 5 days per week for 6 weeks, or to 35 ppm continuously for 90 days (Prendergast et al. 1967); or in rats exposed to 600 ppm 7 hours/day, 5 days per week for 104 weeks (Maltoni et al. 1988).

2.2.1.3 Immunological and Lymphoreticular Effects

It has been suggested that in some cases dermal effects in persons occupationally exposed to trichloroethylene may be a sensitivity reaction (Czirjak et al. 1993; Goh and Ng 1988; Phoon et al. 1984).

Only one study of immunological function in animals after inhalation exposure to trichloroethylene was located. 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. The specific mechanism of the increased susceptibility is unknown. The NOAEL and LOAEL identified in this study are recorded in Table 2- 1 and plotted in Figure 2-l. 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).

2.2.1.4 Neurological 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 2-l. 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 exposures of 2-2.5 hours at 1,000 ppm include impaired visual-motor coordination (measured by groove-type hand steadiness, depth perception, and pegboard tests) (Vernon and Ferguson 1969) and, at 200 ppm, an increase in heart and breathing rates when trichloroethylene was inhaled simultaneously with ethanol ingestion (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 less than 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 each 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 from five to six volunteers exposed to 200 ppm for 5 days, 7 hours/day, although they did complain of fatigue, 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. Based on the LOAEL of 200 ppm observed in humans in the Stewart et al. (1970) study, an acute-duration inhalation MBL of 2 ppm was calculated as described in the footnote in Table 2-l.

In cases of acute occupational exposure, the circumstances are usually accidental and the actual exposure level is unquantified. One such instance resulted in dizziness, loss of facial sensation, and difficulty swallowing (Lawrence and Partyka 1981), while more severe cases of nausea and unconsciousness have also been reported (Lachnit and Pietschmann 1960; Sidorin et al. 1992). Two men collapsed while working for about an hour in a closed room contaminated with trichloroethylene from spilled paint (Longley and Jones 1963). The exposure concentration was estimated to be about 3,000 ppm. A 24-year-old man who breathed air contaminated with an unspecified concentration of trichloroethylene for 15 minutes exhibited trigeminal nerve damage when tested up to 4 months later, as demonstrated by loss of facial sensation. This was manifested by increased thermal and tactile thresholds, altered trigeminal evoked potentials, and increased latency of blink reflex (Leandri et al. 1995). Workers exposed to high levels of trichloroethylene have also noted a feeling of euphoria or giddiness (Feldman 1970; Milby 1968). This is often accompanied by feelings of sleepiness and confusion. Follow-up of an acute exposure case indicated permanent nerve damage

resulting from exposure to an unknown level of trichloroethylene, with residual deficits in neurological functions noted 12-18 years after the exposure (Feldman et al. 1985). These deficits entailed neuro-ophthalmological impairments such as asymmetric pupillary responses and also neuropsychological impairments such as memory deficits. Similar symptoms have been seen in people who have intentionally inhaled high concentrations of trichloroethylene for its intoxicating effects (Clear-field 1970; James 1963; Pembleton 1974; Thierstein et al. 1960; Troutman 1988). This use has led to adverse systemic effects and death, as described elsewhere in this profile. 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.

Trichloroethylene has been 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 has also been used, with variable success, in the treatment of painful symptoms of trigeminal neuralgia (Glaser 1931).

Acute exposure to trichloroethylene and its decomposition products (e.g., dichloroacetylene) has also led to residual neuropathy, characterized by nerve damage. This neuropathy is characterized by facial numbness, jaw weakness, and facial discomfort (indicating damage to cranial nerves V and VII) which can persist for several months (Buxton and Hayward 1967; Feldman 1970). Chronic exposure in the workplace has also been associated with damage to the cranial nerves in several cases (Bardodej and Vyskocil 1956; Barret et al. 1987; Cavanagh and Buxton 1989). Persons who have died from overexposure have shown degeneration of cranial nuclei in the brain stem (Buxton and Hayward 1967). Some of these effects may be attributed to

dichloroacetylene, a decomposition product of trichloroethylene, which may form under nonbiological conditions of heat or alkalinity (Humphrey and McClelland 1944; Saunders 1967). However, it is not yet clear from other reports of cranial nerve damage whether the causal agent was trichloroethylene alone (Buxton and Hayward 1967; Feldman et al. 1985; Leandri et al. 1995; Saunders 1967). Thus, the evidence for associating cranial nerve damage with exposure to trichloroethylene itself remains equivocal.

Intermediate and chronic exposures of workers 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 trigeminal nerve impairment as measured by blink reflex, but did observe a significant association between years of exposure and masseter reflex, which is another measure of trigeminal nerve function (Ruitjen 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 l-2 hours per 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.

Other reported neurological effects of chronic occupational exposure to unquantified trichloroethylene levels include memory loss (Grandjean et al. 1955; Smith 1966), mood swings (Barr-et et al. 1987; Milby 1968; Rasmussen et al. 1993d), trigeminal neuropathy (Bar-ret et al. 1987; Feldman et al. 1992; Mitchell and Parsons-Smith 1969; Smith 1966), cranial nerve VII 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 a significant effect, including the facial (Feldman et al. 1985), olfactory (Rasmussen et al. 1993a), and acoustic nerves. Interestingly, the study by Rasmussen et al. (1993a) found no significant association between length of exposure and trigeminal nerve effect, although a nonsignificant trend was seen, indicating that the sample size may have simply been too small.

Studies on the neurological effects of acute trichloroethylene inhalation in animals have produced results similar to human studies. In rats, exposures of 8 hours or less 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 per day, 5 days per week for 10 days (Goldberg et al. 1964b). No neurological effects were observed at 1,568 ppm. 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 l l-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).

A study that examined the interaction between exposure concentration and time of exposure on nervous system function found that concentration, rather than time of exposure, was more important in determining effects (Bushnell 1997). Rats were trained to press two levers for food reward; one lever when a light flashed, the second lever produced food when there was no signal. 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.

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). 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 per day 5 days per 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 Fischer-344 rats exposed for 3 weeks to 2,000 ppm and to 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. Fischer-344 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 (Albee et al. 1993). Altered flash evoked potentials were not observed in rats exposed to 250 ppm.

After 10 days of exposure, reduced social behavior and reduced exploratory behavior were observed in rats exposed to 100 ppm trichloroethylene 6 hours per day 5 days per week for a total of 5 weeks (Silverman and Williams 1975). 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 after exposure of 100 ppm (Arito et al. 1994a). Based on the 50-ppm LOAEL identified in the Arito et al. (1994a) study, an intermediate-duration inhalation MRL of 0.1 ppm was calculated as described in the footnote in Table 2-l.

In a study involving 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 &hour exposure to 300 ppm of trichloroethylene, followed by exposure to 1,000 ppm for 8 hours 7 days later (Arito et al. 1994b). 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 per day, 5 days per 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 per day, 5 days per week for 30 days (Goldberg et al. 1964a). Changes in visually evoked potentials (Blain et al. 1992) and electroretinal responses to flash stimulation (Blain et al. 1994) were seen in rabbits exposed to 350 ppm trichloroethylene for 12 weeks (4 days/week, 4 hours/day). The study authors suggested that binding of trichloroethanol to blood proteins may enable it to reach the visual cortex.

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 for 4 days, 6 hours a day, to 200 ppm (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 deoxyribonucleic acid (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 2- 1 and plotted in Figure 2- 1.

2.2.1.5 Reproductive Effects

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.

Mice exposed to 2,000 ppm of trichloroethylene, 4 hours/day for a 5-day period, had a significant increase in abnormal sperm morphology of 1% 28 days after the exposure (Land et al. 1981). No effect was seen at 200 ppm. 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 per 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 these 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 2- 1 and plotted in Figure 2- 1.

2.2.1.6 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 (TCE). This risk increased further when women with less than l/2 hour of exposure to TCE 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 TCE. 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 analyze TCE exposures and most fetal growth would occur after the first 20 weeks of pregnancy.

Pregnant laboratory animals have been exposed to trichloroethylene vapors, but no conclusive studies have been encountered that clearly indicate teratogenic effects. Available data from animals suggest that the conceptus is not uniquely susceptible to trichloroethylene (EPA 1985c). No statistically significant increases in skeletal, visceral, or external malformations have been found in pups of rat dams exposed to 100-500 ppm of trichloroethylene (Beliles et al. 1980; 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 per day on gestation days 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 per day on gestation days 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 2-l or Figure 2-l.

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 2-1 and plotted in Figure 2- 1.

2.2.1.7 Genotoxic Effects

Investigations into the genotoxicity of trichloroethylene in humans have not been conclusive but are suggestive of clastogenic effects. A study of chromosomal aberrations among trichloroethylene-exposed workers detected an increase in hypodiploid cells but found no evidence of chromosomal breaks in lymphocytes (Konietzko et al. 1978). Another study showed an increase in sister chromatid exchange for workers exposed to trichloroethylene (Gu et al. 1981). In a more recent study, men using trichloroethylene as a degreasing agent were tested for lymphocyte chromosomal abnormalities- specifically, breaks, gaps, deletions, inversions, translocations, and hyperdiploidy. The same study also investigated the rate of nondisjunction for the Y chromosome in sperm. Positive results were observed for chromosomal aberrations and hyperdiploid cells, but the results were negative for chromosomal nondisjunction (Rasmussen et al. 1988). The frequency of sister chromatid exchange in the peripheral lymphocytes of trichloroethyleneexposed workers was the focus of another investigation (Seiji et al. 1990). Smokers and nonsmokers were included in this study. The only positive result obtained was for smokers who were also exposed to trichloroethylene. Since smoking itself is known to induce sister chromatid exchange, sister chromatid exchange comparisons were performed among smokers and nonsmokers irrespective of trichloroethylene exposure. This general comparison between smokers and nonsmokers showed no significant differences in the rate of sister chromatid exchange. Therefore, the study authors suggest that smoking and trichloroethylene exposure may act together to produce increased sister chromatid exchange frequencies (Seiji et al. 1990). The study authors point out that other compounds (i.e., toluene and styrene) show synergisms with smoking. This study is limited by a relatively small sample size (26 male and 25 female nonsmokers; 22 male and 16 female smokers). In addition, it was unclear whether exposure to other solvents also occurred. Finally, other researchers have found no significant increase in the rate of sister chromatid exchange among either smoking or nonsmoking workers exposed to trichloroethylene (Nagaya et al. 1989a).

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 tumor induction by trichloroethylene than rats. 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.

Other genotoxicity studies are discussed in Section 2.5.

2.2.1.8 Cancer

Several retrospective cohort studies of workers exposed to unquantified levels of trichloroethylene have been conducted. All of these studies have limitations that restrict their usefulness for evaluating the carcinogenicity of trichloroethylene. None has shown clear, unequivocal, evidence that trichloroethylene exposure is linked to increased cancer risk.

A number of epidemiological studies have been conducted to investigate human exposure to trichloroethylene in the workplace and subsequent tumor development (Axelson 1986; Axelson et al. 1978, 1994; Malek et al. 1979; Shindell and Uhich 1985; Spirtas et al. 1991). These investigators did not find significant increases in incidence of cancer, but some studies were limited by relatively small numbers of subjects, lack of lengthy follow-up periods, and multiple chemical exposure. When all workers (14,457) at an aircraft maintenance facility were studied, significant increases in multiple myeloma in white women (standardized mortality ration [SMR] 236; 95% confidence interval [CI] 87-514), non-Hodgkin’s lymphoma in white women (SMR 2 12; 95% CI 102-390), and cancer of the biliary passages and liver in white men dying after 1980 (SMR 358; 95% CI 116-836) were observed. When only those exposed to trichloroethylene were examined (6,929) no

significant associations between several measures of trichloroethylene exposure and excess cancer risk were observed. For example, based on 4 cases of non-Hodgkin's lymphoma among white women exposed to trichloroethylene, the SMR was 286 with a 95% CI of 78-731. The study authors pointed out that the work histories of persons dying from multiple myeloma or non-Hodgkin's lymphoma indicated that many of the women who developed these diseases worked in fabric handling departments where a substance used to treat fabric ("dope") and solvents were used. The study authors concluded that "no significant or persuasive relationships were found between various measures of exposure to trichloroethylene and the risk of any specific malignancy."

An update of a previous study (Axelson et al. 1978), Axelson (1986) evaluated an expanded cohort of 1,424 men (levels of trichloroethylene exposure inferred from measured urinary metabolite concentrations) and found a significant increase in incidences of bladder cancer and lymphomas, and a lower than expected incidence of total cancer mortality. A further update of this work (Axelson et al. 1994) expanded the cohort to include 249 women, tracking cancer morbidity over 30 years, and found no correlation between exposure concentration or exposure time and cancer incidence at any site. The highest standardized incidence ratio noted in this study was 1.56 (95% CI of 0.51-3.64) for 5 cases of non-Hodgkin's lymphoma observed in men. Although four of these cases occurred in persons exposed for at least 2 years, and 3 cases had a latency of 10 years or more, urinary levels of TCA showed that 4 of the 5 cases were exposed to the lowest levels of trichloroetbylene (urinary levels of TCA 0 - 49 mgL). The study authors mentioned that a urinary TCA level below 50 mg/L corresponds to a trichloroethylene exposure concentration of about 20 ppm. The study authors concluded that "this study provides no evidence that trichloroethylene is a human carcinogen, i.e., when the exposure is as low as for this study population."

In contrast, three European studies have found slight but statistically significant increases in cancer in workers exposed to trichloroethylene. A survey of Finnish workers exposed to primarily trichloroethylene found an association of limited statistical significance between exposure and incidence of stomach, liver, prostate, and lymphohematopoietic cancers (Antilla et al. 1995). However, the study did not reliably separate the effects of individual solvents, so attributing these cancers to trichloroethylene exposure alone was not possible. A significant association between workplace exposure to trichloroethylene and kidney cancer was found in a retrospective cohort study of German cardboard factory workers (Henschler et al. 1995). The

association was based on five cases of kidney cancer among 169 workers who had been exposed to trichloroethylene for at least 1 year (mean exposure period = 17.8 years) between 1956 and 1975, relative to no cases among the unexposed control group. Exposure levels were not provided in this study. In a study of Swedish workers, a statistically significant increase in non-Hodgkin's lymphoma was observed (Hardell et al. 1994). This study utilized univariate analysis of 105 confirmed cases of non-Hodgkin's lymphoma and found an increased risk of non-Hodgkin's lymphoma associated with occupational exposure to trichloroethylene. These workers were exposed to solvents in addition to trichloroethylene, and exposures were self-reported. A study of dry cleaners found a significant increase in the incidence of all malignant neoplasms combined as well as increased incidences of cancer at several sites (lung/bronchus/trachea, cervix, and skin) (Blair et al. 1979). Exposure to trichloroethylene, however, was not well documented; evidence indicates that exposures were primarily to tetrachloroethylene and other dry-cleaning chemicals (e.g., carbon tetrachloride, petroleum solvents). Thus, the human studies that did show increases in cancer are limited by uncertainties in the exposure data, small sample sizes, and likely exposure to other chemicals. In other studies, associations between liver cancer (Novotna et al. 1979; Paddle 1983) and trichloroethylene exposure have not been observed.

Some laboratory studies with rats and mice have linked trichloroethylene exposure to various types of cancers. Several of these studies, however, should be viewed cautiously, since the tumorigenic activity might be influenced by the presence of direct-acting compounds, namely the epoxides (e.g., epichlorohydrin) added as stabilizers in trichloroethylene. Epoxides are known to be very reactive, and some, such as epichlorohydrin, are potent carcinogens themselves.

Increased incidence of hepatomas (specific type of neoplasm not specified) occurred in male Swiss mice and in $B6C3F_1$ 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 (Maltoni et al. 1986, 1988). In a retest with male $B6C3F_1$ mice, a decrease in leukemias was seen, 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 $B6C3F_1$ mice but not among the males. Incidences were significantly increased over controls at 600 ppm for lung tumors in the female $B6C3F_1$ mice and at 600 ppm for liver tumors in both sexes of $B6C3F_1$ mice. The incidence data

for lung tumors in female Swiss mice together with other tumor incidence data from other studies were used by EPA (1987a) to derive a carcinogenic potency estimate; a classification of B2 (probable human carcinogen) was assigned to trichloroethylene. In 1988, EPA's Scientific Advisory Board offered an opinion that the weight of evidence was on a C-B2 continuum (possible-probable human carcinogen). The agency has not restated a more current position on the weight-of-evidence classification and is reflecting this by posting an "under review" status in the Integrated Risk Information System (IRIS) (IRIS 1996).

In male Sprague-Dawley rats, there was a dose-related increase in testicular Leydig cell tumors and a slight increase in tubular renal adenocarcinoma at the 600-ppm exposure level after exposure for 104 weeks (Maltoni et al. 1986, 1988). EPA and other groups regard such increases as indicative of a hazard potential unless there are reasons to rule this out. However, other authorities believe testicular tumors are common in rats that are not exposed to toxic substances.

There are several problems in interpreting these studies. First, males and females responded differently; in some cases, the females were more sensitive, but in others, the males were more sensitive. In addition, there were lung and liver tumors in mice but not rats. An inconsistency was also observed in the two different studies with $B6C3F_1$ male mice. In one study, an increase in hepatomas was reported, whereas no significant increase was seen in the other. In addition, an inconsistent dose-response was observed, i.e., an increase in liver tumors at high levels, and a decrease compared to control levels at the low dose. Other problems were found in the study methodology: use of an unconventional technique of holding the animals until spontaneous death, use of an unorthodox method of reporting results (percentage of animals with tumors reported, but not the number of surviving animals), a lack of appropriate pathological data on the types of tumors observed, and a lack of a complete report on methodology. Finally, inadequate laboratory operation procedures were used; there was a lack of independent pathology reviewers; and the use of Good Laboratory Practices was not confirmed.

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. The amount of epichlorohydrin (approximately 0.019%) was extremely low in this

study. It should be recognized that some types of cells in the lung have the ability to metabolize trichloroethylene and that metabolic activation *in situ* may be responsible for the pulmonary injury and carcinogenicity seen following inhalation exposure (Bruckner et al. 1989).

Two other inhalation carcinogenicity studies were negative. Newborn rats were exposed to 2,000 ppm trichloroethylene for 10 weeks, but examination of the liver showed no signs of ATPase-deficient foci (Laib et al. 1979). This apparent preneoplastic change was seen in the liver of rats similarly exposed to vinyl chloride, a known hepatocarcinogen. NMRI mice, Wistar rats, and Syrian hamsters of both sexes were exposed to 100 or 500 ppm of trichloroethylene for 18 months (Henschler et al. 1980). The only statistically significant effect was an increase in the incidence and rate of development of malignant lymphomas in female mice over controls. 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 cancer effect levels (CELs) in Table 2- 1 and Figure 2- 1.

2.2.2 Oral Exposure

2.2.2.1 Death

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

Acute oral LD_{50}s 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 gestation days 6-152 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 (Met-rick et al. 1989). Further

explanation of these study results is included in Section 2.2.2.2, 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 2.2.2.8. LD_{50} values and the lowest doses causing death in rats and mice are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.2 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 2-2 and plotted in Figure 2-2.

Respiratory Effects. 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 Wobum, Massachusetts, were found to contain several solvents including trichloroethylene (267 ppb) and 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 2.2.2.8.

Rales and dyspnea were observed in pregnant rats treated by gavage with 1,500 mg/kg/day trichloroethylene in corn oil on gestation days 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.

TABLE 2-2. Levels of Significant Exposure to Trichloroethylene - Oral

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
ACUTE EXPOSURE							
Death							
1	Rat (Sprague-Dawley)	Gd 6-15 (GO)				1125 F (2/13 died)	Narotsky et al. 1995
2	Rat (NS)	once (G)				7208 (LD_{50})	Smyth et al. 1969
3	Mouse (CD-1)	once (G)				2443 F (LD_{50}) 2402 M (LD_{50})	Tucker et al. 1982
Systemic							
4	Rat (Fischer-344)	14 d (GO)	Hepatic	500 F	1500 F (increased relative liver weights, hepatocellular hypertrophy)		Berman et al. 1995
			Renal		50 F (increased relative kidney weights)		
			Endocr	1500 F			

TABLE 2-2. Levels of Significant Exposure to Trichloroethylene - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
5	Rat (Wistar)	10 d 1 x/d (GO)	Hepatic	2000M			Elcombe 1985
6	Rat (Fischer-344)	10 d 1 x/d (GO)	Hepatic		1000M (122% increased liver weight, 180% increased palmitoyl CoA oxidation activity)		Goldsworthy and Popp 1987
			Renal	1000M			
			Bd Wt	1000M			
7	Rat (Fischer-344)	10 d 1 x/d (GO)	Renal	1000			Goldsworthy et al. 1988
8	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)	
9	Rat (Sprague-Dawley)	Gd 6-15 (GO)	Bd Wt			475 F (body weight gain 31% lower than controls)	Narotsky et al. 1995

TABLE 2-2. Levels of Significant Exposure to Trichloroethylene - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
10	Rat (Osborne-Mendel)	3 d 1 x/d (GO)	Hepatic	1100M			Stott et al. 1982
			Renal	1100M			
11	Mouse (Swiss-Webster)	10 d 1 x/d (GO)	Hepatic	50M	100M (200% increase in palmitoyl CoA oxidation)		Elcombe 1985
12	Mouse (B6C3F1)	10 d 1 x/d (GO)	Hepatic		1000M (150% increased liver weight, 625% increased palmitoyl CoA oxidation activity)		Goldsworthy and Popp 1987
			Renal	1000M			
			Bd Wt	1000M			
13	Mouse (B6C3F1)	3 d 1 x/d (GO)	Hepatic		2400M (hepatic hypertrophy, centrilobular swelling)		Stott et al. 1982
			Renal	2400M			

TABLE 2-2. Levels of Significant Exposure to Trichloroethylene - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
14	Mouse (CD-1)	14 d 1 x/d (G)	Hemato	240M			Tucker et al. 1982
			Hepatic	240M			
			Renal	240M			
			Bd Wt	240M			
Neurological							
15	Rat (Fischer-344)	14 d (GO)		150 F	500 F (increased rearing)		Moser et al. 1995
16	Rat (Sprague-Dawley)	Gd 6-15 (GO)		475 F		633 F (transient ataxia)	Narotsky et al. 1995
Developmental							
17	Rat (Sprague-Dawley)	Gd 6-15 (GO)		844		1125 (increased prenatal loss, micro- or anophthalmia)	Narotsky et al. 1995
18	Mouse (B6D2F1)	Gd 1-5 Gd 6-10 Gd 1-15 1 x/d (GO)		240			Cosby and Dukelow 1992

TABLE 2-2. Levels of Significant Exposure to Trichloroethylene - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
19	Mouse (NMRI)	7 d 1 x/d (GO)			50[b] M (reduced rearing rate at 60 days of age)		Fredriksson et al. 1993
INTERMEDIATE EXPOSURE							
Death							
20	Rat (Osborne-Mendel)	6 wk 5 d/wk 1 x/d (GO)				5620 (10/10 died)	NCI 1976
21	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
22	Mouse (B6C3F1)	6 wk 5 d/wk 1 x/d (GO)				5620 M (4/5 deaths) 3160 F (2/5 deaths)	NCI 1976
23	Mouse (B6C3F1)	13 wk 5 d/wk 1 x/d (GO)				1500 M (2/10 died) 3000 F (1/10 died)	NTP 1990

TABLE 2-2. Levels of Significant Exposure to Trichloroethylene - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
Systemic							
24	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	2000M			
			Gastro	2000M			
			Musc/skel	2000M			
			Hepatic	2000M			
			Renal		1000 F (minimal or mild cytomegaly, karyomegaly of renal tubular epithelial cells in 5/10)		
			Endocr	2000M			
			Derm	2000M			
			Bd Wt	1000M		2000 M (body weights 24% less than controls)	
25	Rat (Osborne-Mendel)	3 wk 5 d/wk 1 x/d (GO)	Hepatic	1100M			Stott et al. 1982
			Renal	1100M			
			Bd Wt	1100M			
26	Mouse (Swiss-Cox)	6 wk 5 d/wk 1 x/d (GO)	Hepatic	100M	400M (enlarged hepatocytes)	1600 M (central lobular necrosis)	Buben and O'Flaherty 1985
			Bd Wt	3200			

TABLE 2-2. Levels of Significant Exposure to Trichloroethylene - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
27	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	2400M			
28	Mouse (B6C3F1)	3 wk 5 d/wk 1 x/d (GO)	Hepatic	250M	500M (liver enlargement, increased DNA content per gram tissue)	1200 M (liver enlargement, increased DNA content, centrilobular hepatocyte swelling)	Stott et al. 1982
			Renal	2400M			
			Bd Wt	2400M			
29	Mouse (CD-1)	6 mo ad libitum (W)	Gastro	18 M 793 F	217M (gas pockets in the intestinal coating, blood in the intestines in 5)		Tucker et al. 1982
			Hemato	393 M 793 F	660M (red blood cell counts 16% lower than controls)		
			Hepatic	793 F			
			Renal	217 M 437 F	393 M (elevated urinary 793 F protein and ketones)		
			Bd Wt	393M	660M (body weights 11% lower than controls, associated with decreased water intake)		

TABLE 2-2. Levels of Significant Exposure to Trichloroethylene - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
Immunological/Lymphoreticular							
30	Mouse (CD-1)	4 or 6 mo ad libitum (W)		200 F	400 F (suppressed humoral and cellular response)		Sanders et al. 1982
Neurological							
31	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
32	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
Reproductive							
33	Rat (Fischer-344)	18 wk ad libidum (F)		300			NTP 1986

TABLE 2-2. Levels of Significant Exposure to Trichloroethylene - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
34	Rat (Long-Evans)	6 wk 5 d/wk 1 x/d (GO)		100M		1000 M (impaired copulatory behavior, mount/ ejaculation latency, intromissions)	Zenick et al. 1984
35	Mouse (CD-1)	17 wk ad libitum (F)		375M 750 F	750M (18-45% decreased sperm motility)		NTP 1985
Developmental							
36	Rat (Sprague-Dawley)	3 mo before Gd 0-21 ad libitum (W)				0.18 (5% increased fetal heart abnormalities)	Dawson et al. 1993
37	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

TABLE 2-2. Levels of Significant Exposure to Trichloroethylene - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)		Reference
38	Rat (Long-Evans)	2 wk 5 d/wk Gd 0-21 7 d/wk (GO)		100		1000	(decreased neonatal survival)	Manson et al. 1984
39	Rat (Fischer-344)	18 wk ad libidum (F)		300				NTP 1986
40	Rat (Sprague-Dawley)	14 d before mating Gd 0-21 -weaning ad libitum (W)			37M (increased exploratory behavior)			Taylor et al. 1985
41	Mouse (CD-1)	17 wk ad libitum (F)		375M		750	(increased perinatal mortality)	NTP 1985

CHRONIC EXPOSURE

TABLE 2-2. Levels of Significant Exposure to Trichloroethylene - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
Death							
42	Rat (Osborne-Mendel)	78 wk 5 d/wk 1 x/d (GO)				1097 M (47/50 died) 549 F (35/48 died)	NCI 1976
43	Rat (Fischer-344)	103 wk 5 d/wk 1 x/d (GO)				500 M (30/50 died) 500 F (17/50 died)	NTP 1990
44	Mouse (B6C3F1)	78 wk 5 d/wk 1 x/d (GO)				869 F (8/50 died)	NCI 1976
45	Mouse (B6C3F1)	103 wk 5 d/wk 1 x/d (GO)				1000 M (34/50 died)	NTP 1990

TABLE 2-2. Levels of Significant Exposure to Trichloroethylene - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
Systemic							
46	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	50M	250M		
			Endocr	250			
			Derm	250			
			Ocular	250			
			Bd Wt	250			

TABLE 2-2. Levels of Significant Exposure to Trichloroethylene - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
47	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			
			Derm		549 (alopecia, roughening of hair coat, sores)		
			Ocular		549 (squinting, red discharge)		
			Bd Wt	549M	1097M (body weights 18% lower than controls at 78 weeks)		
					549 F (body weights 15% lower than controls at 78 weeks)		

TABLE 2-2. Levels of Significant Exposure to Trichloroethylene - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
48	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			
			Derm	1000			
			Ocular	1000			
			Bd Wt		500M (body weights 11% lower than controls)		
49	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			
			Derm	1000			
			Ocular	1000			
			Bd Wt	500M	1000M (body weights 11.6% lower than controls)		

TABLE 2-2. Levels of Significant Exposure to Trichloroethylene - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
50	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			
			Derm	1000			
			Ocular	1000			
			Bd Wt	500M	1000M (body weights 12.3% lower than controls)		
51	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			
			Derm	1000			
			Ocular	1000			
			Bd Wt	500 F	1000 F (body weights 10.1% lower than controls)		

TABLE 2-2. Levels of Significant Exposure to Trichloroethylene - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
52	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			
			Derm	1000			
			Bd Wt	500M	1000M (body weights 13% lower than controls) 500 F (body weights 12% lower than controls)		
53	Mouse (B6C3F1)	78 wk 5 d/wk 1 x/d (GO)	Resp	2239M			NCI 1976
			Cardio	2239M			
			Gastro	2339M			
			Musc/skel	2239M			
			Hepatic	2239M			
			Renal		1160 M (toxic nephrosis) 869 F		
			Endocr	2239M			
			Derm		869 F (alopecia, skin sores)		
			Ocular	2239M			
			Bd Wt	2239M			

TABLE 2-2. Levels of Significant Exposure to Trichloroethylene - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
54	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			
			Derm	1000			
			Bd Wt		1000 M (body weights 10% lower than controls)		
Cancer							
55	Rat (Fischer-344)	103 wk 5 d/wk 1 x/d (GO)				1000 M (CEL: renal tubular cell adenocarcinomas)	NTP 1990
56	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 2-2. Differences in levels of health effects and cancer effects between males and femalse are not indicated in Figure 2-2. Where such differences exist, only the levels for the most sensitive gender are presented.

[b]Used to derive an acute-duration oral Minimal Risk Level (MRL) of 0.2 mg/kg/day for trichloroethylene; 50 mg/kg/day divided by an uncertainty factor of 300 (10 for using a LOAEL, 10 for extrapolation from animals to humans, and 3 for human variability, to account for differences in metabolism, and considering pups as a sensitive subpopulation) .

Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; CoA = coenzyme A; d = day(s); Derm = dermal; DNA = deoxyribonucleic acid; Endocr = endocrine; F = female; (F) = food; Gastro = gastrointestinal; (G) = gavage (type unspecified); Gd = gestation day(s); (GO) = gavage in oil; (GW) = gavage in water; Hemato = hematological; LOAEL = lowest-observed-adverse-effect level; LD_{50} = lethal dose, 50% kill; M = male; mo = months; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; (W) = drinking water; wk = week(s); x = time(s)

Figure 2-2. Levels of Significant Exposure to Trichloroethylene - Oral

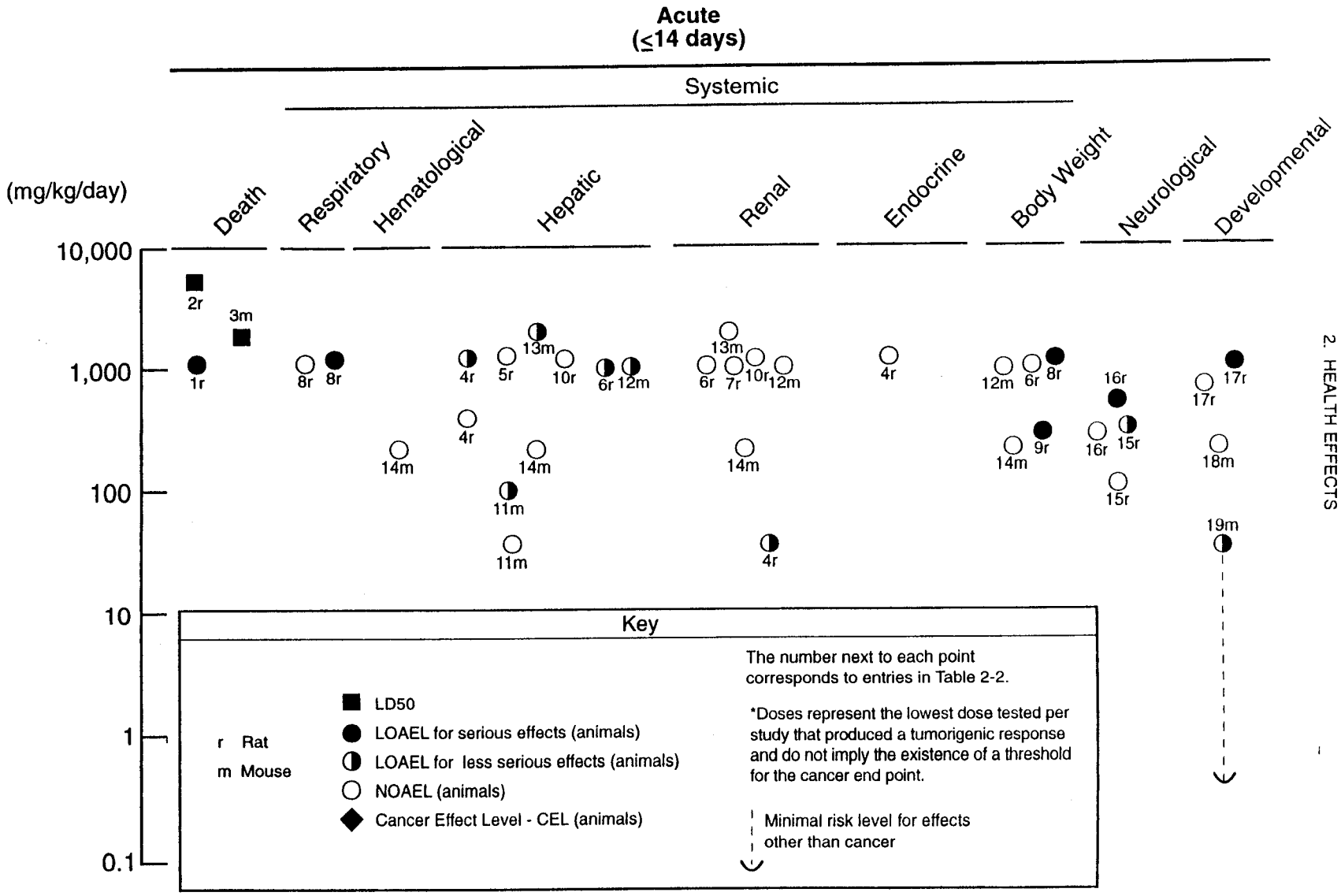


Figure 2-2. Levels of Significant Exposure to Trichloroethylene - Oral (continued)

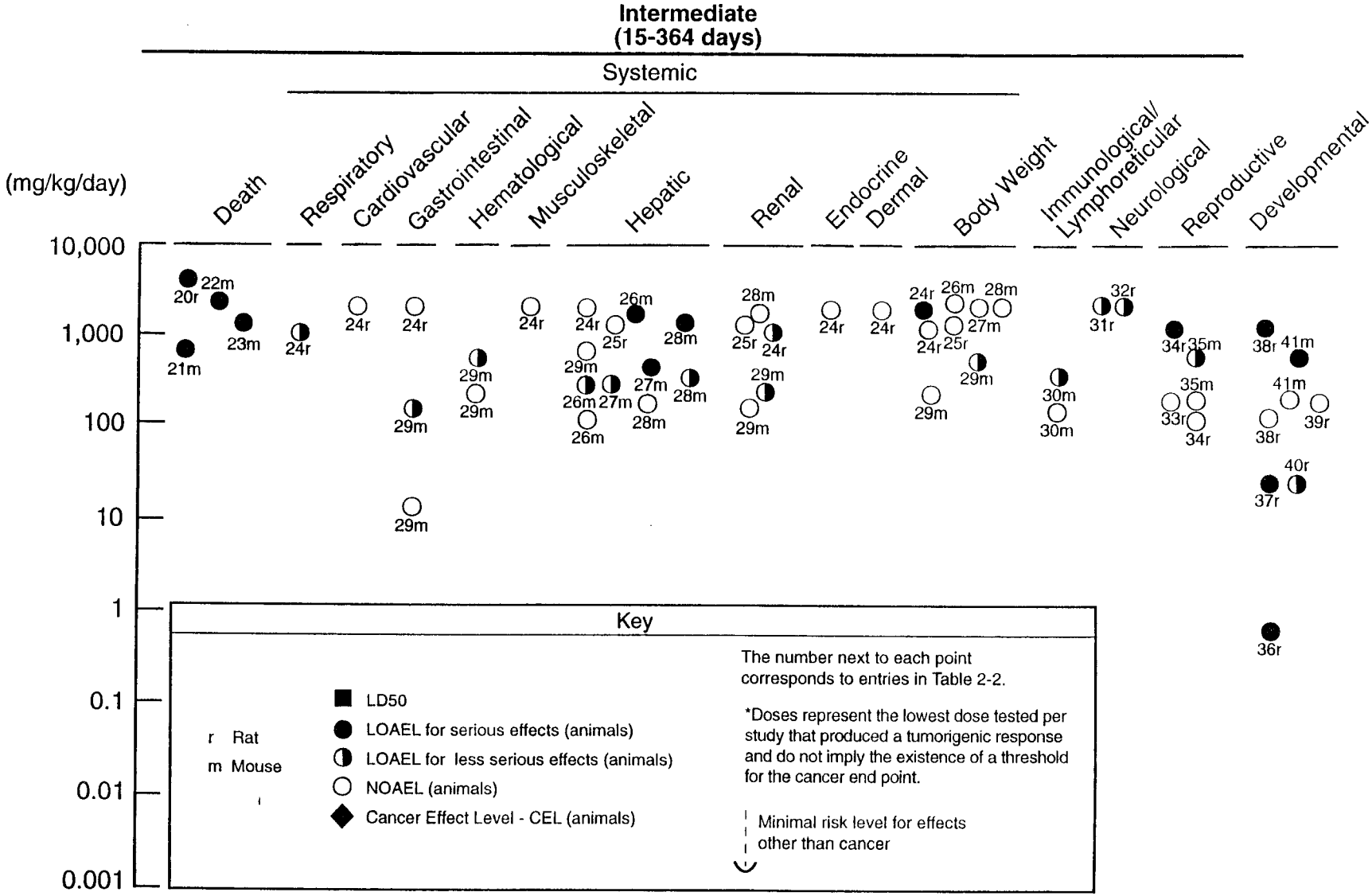


Figure 2-2. Levels of Significant Exposure to Trichloroethylene - Oral (continued)

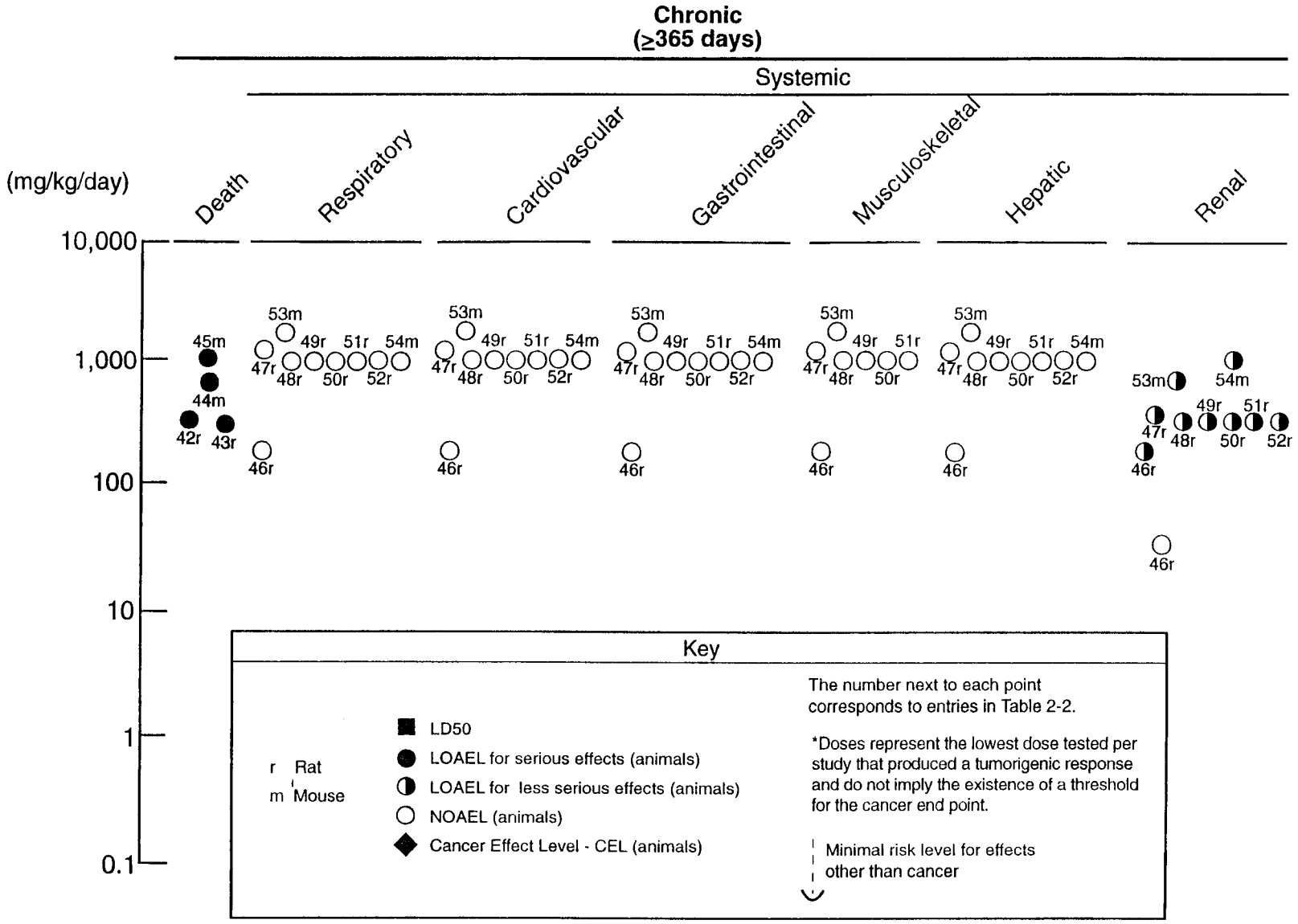
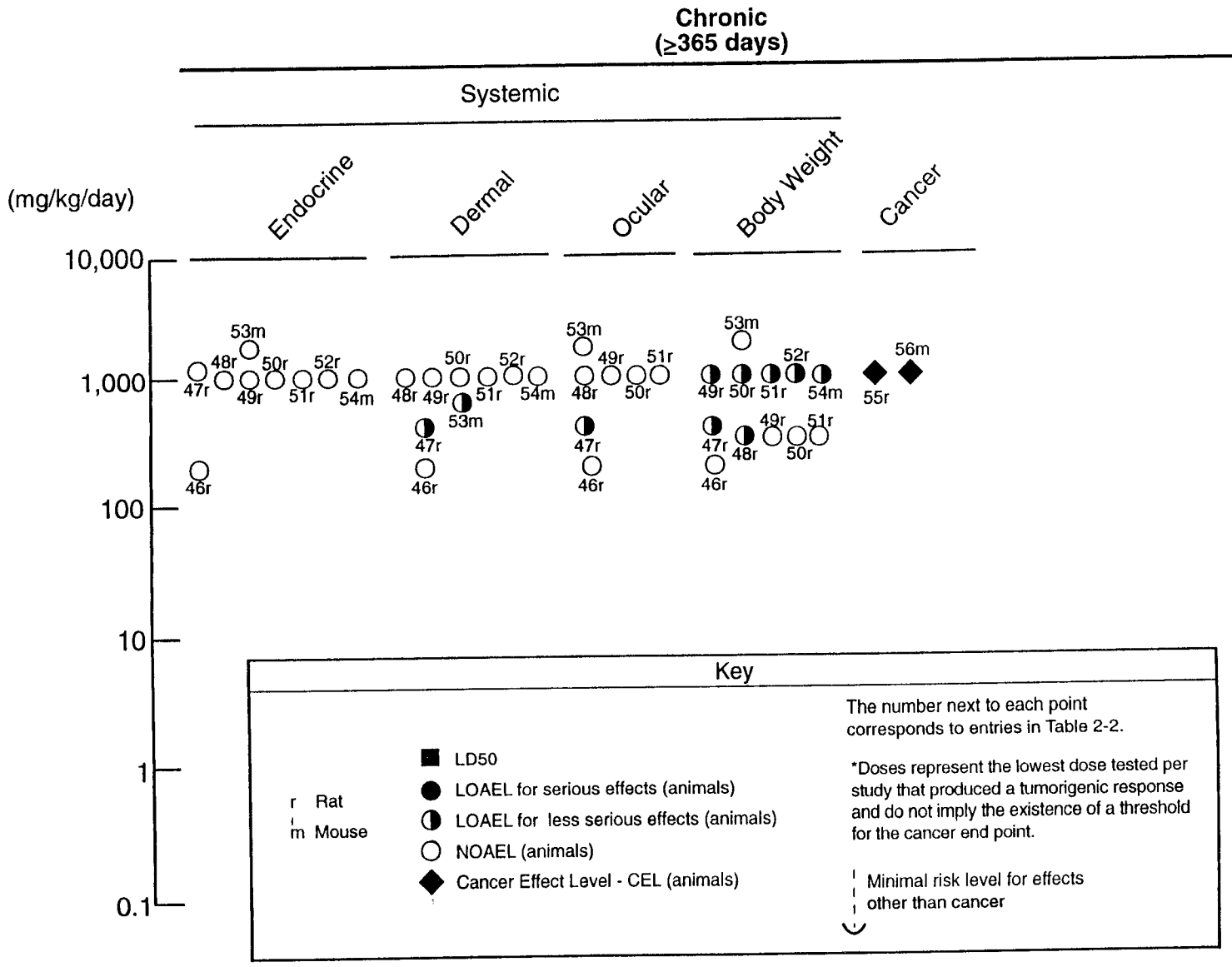


Figure 2-2. Levels of Significant Exposure to Trichloroethylene - Oral (continued)



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 a women who drank an unknown amount of trichloroethylene (Perbellini et al. 1991).

Cardiovascular effects of trichloroethylene were investigated in families from Wobum, Massachusetts, that included at least one child with leukemia (Byers et al. 1988). Medical and laboratory tests were conducted on 25 family members. There were 14 surviving parents, all of whom 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 2.2.2.8. Excesses of anemia, stroke, blood disorders, and death from heart disease were reported in the ATSDR subregistry of persons environmentally exposed to trichloroethylene (ATSDR 1994; Burg et al. 1995). However, the data were gathered by questionnaire and may be limited by reporting bias.

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. 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 2.2.2.8. Self-reported gastrointestinal problems were not increased among persons in the trichloroethylene subregistry who were exposed to trichloroethylene in their drinking water (ATSDR 1994; Burg et al. 1995).

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 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 a 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 2.2.1.2).

Histopathological changes in the gastrointestinal tract have not been observed in intermediate- or chronic-duration studies in which rats and mice were treated by gavage to 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 mgLkg/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. The trichloroethylene subregistry, which has compiled information on 4,280 people exposed to trichloroethylene through their drinking water, found significantly increased incidences of anemia in selected age groups when compared with corresponding national data (ATSDR 1994; Burg et al. 1995). The excess rates did not show a pattern with respect to age or sex. Therefore, no conclusion regarding the association between trichloroethylene and hematological effects can be drawn from this study.

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).

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. No 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). Self-reported liver problems were not increased among persons in the trichloroethylene subregistry who were exposed to trichloroethylene in their drinking water (ATSDR 1994; Burg et al. 1995).

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 (Stott et al. 1982). Liver effects were not observed in rats treated with three daily gavage doses of 1,100 mg/kg trichloroethylene in corn oil (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 (Elcombe 1985). Significant dose-related effects on peroxisomal β-oxidation activity were not observed in rats treated for 10 days by gavage with trichloroethylene in corn oil at doses up to 2,000 mg/kg/day (Elcombe 1985). A second lo-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 p-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 (Dees and Travis 1993). The study authors suggest that trichloroethylene induces mitosis and DNA proliferation in mature hepatocytes.

Several studies did show 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 glutamic-pyruvic transaminase (SGPT) 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. Liver effects were not observed in rats treated by gavage with trichloroethylene in corn oil at 1,100 mg/kg/day for 3 weeks (Stott et

al. 1982). 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). 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).

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 793 mg/kg/day) for 6 months, showed no treatment-related effects other than increased liver weights without accompanying macroscopic lesions (Tucker et al. 1982). This may be indicative of differences in absorption efficiencies of the lipophilic trichloroethylene administered in water versus oil.

In contrast to mice, 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). 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). Except for enlarged livers, liver effects were not reported in mice treated by gavage with trichloroethylene in corn oil for 18 months at a dose of 1,978 mg/kg/day for males and 1,483 mg/kg/day for females (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).

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 is available that 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, three communities in Michigan that were exposed to trichloroethylene and other solvents in drinking water had no increase in kidney disease (Freni and Bloomer 1988).

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 pahnitoyl 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-2_u-globulin in the kidneys of male rats when 1,000 mg/kg/day trichloroethylene was similarly administered to male and female Fischer-344 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). Increased kidney weights, but no histopathological changes were observed in rats treated by gavage with 1,500 but not 500 mg/kg/day trichloroethylene in corn oil (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 Osbome-Mendel rats (approximately 550-1,100 mg/kg/day) and B6C3F_1 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 AC1 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 2.2.2.8.

Endocrine Effects. No studies were located regarding endocrine effects in humans following oral exposure to trichloroethylene.

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; NIT 1988, 1990).

Dermal Effects. Some of the people in Wobum, 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 24 weeks. These skin conditions generally ceased l-2 years after cessation of exposure to contaminated water. The limitations of this study are discussed in Section 2.2.2.8. 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 fascitis, 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 improved symptoms.

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 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 trichlorethylene.

Squinting and a red discharge from the eyes were reported with increasing frequency in rats treated by gavage with trichloroethylene in corn oil at time-weighted average 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 chronicduration 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. No effects on body weight were observed in rats or mice treated by gavage with trichloroethylene in corn oil at a dose of 1,000 mg/kg/day for 10 days (Goldsworthy and Popp 1987). In pregnant rats treated by gavage with trichloroethylene in corn oil, body weight gain was 45% lower than controls in rats treated with 1,125 mg/kg/day on gestation days 6-19 (Narotsky and Kavlock 1995) and 31% lower than controls in rats treated with 475 mg/kg/day on gestation days 6-15 (Narotsky et al. 1995).

Body weight effects were not observed in mice treated with trichloroethylene by gavage at a dose of 240 mg/kg/day for 14 days or in drinking water at a dose of 660 mg/kg/day for 6 months (Tucker et al. 1982). Body weight effects were also not observed in mice following gavage treatment at a dose of 2,400 mg/kg/day for 3 (Stott et al. 1982) or 4 weeks (Merrick et al. 1989) or a dose of 3,200 mg/kg/day for 6 weeks (Buben and O'Flaherty 1985). No effect on body weight was observed in rats treated by gavage with a dose of 1,100 mg/kg/day for 3 weeks (Stott et al. 1982) or a dose of 1,000 mg/kg/day for 13 weeks (NTP 1990). Body weights were 24% less than controls in rats treated by gavage with trichloroethylene in corn oil at a dose of 2,000 mg/kg/day for 13 weeks (NTP 1990).

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 tricbloroethylene 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).

2.2.2.3 Immunological and Lymphoreticular Effects

Immunological abnormalities were reported in 23 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 2.2.2.8. 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 (arthritis, Raynaud's phenomenon, malar rash, skin lesions related to sun exposure, seizure or convulsions) of which were statistically significant (Kilbum and Warshaw 1992). Diffuse fascitis 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).

The immunotoxic effects of trichloroethylene were evaluated in CD- 1 mice following sensitization to sheep red blood cells during exposure to trichloroemylene for 14 days by gavage (at 24 or 240 mg/kg) or for 4 and 6 months in drinking water (at doses of 18-800 mg/kg) (Sanders et al. 1982). The parameters assessed included humoral and cell-mediated immunity, lymphocyte responsiveness to mitogens, bone marrow function, and macrophage function. A significant inhibition of cell-mediated immunity of males exposed via gavage was noted, while the antibody-mediated immune response remained similar to vehicle-treated controls; no females were involved in this phase of the study. In the drinking water study, observed effects

included depression of delayed type hypersensitivity in males (67% depression at the high dose of 660 mg/kg). Antibody-mediated immunity was significantly inhibited in females only, and significant only at 400 and 700 mg/kg, in a dose-response fashion. Overall, females were seen to be more sensitive. The effects seen were consistent with effects of other chlorinated hydrocarbons on the immune system. 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 investigators concluded that, although the effects observed were not remarkable, the immune system does appear to be sensitive to the chemical. The NOAEL and LOAEL for immunological effects in mice identified in the Sanders et al. (1982) study are recorded in Table 2-2 and plotted in Figure 2-2.

Histopathological changes in the spleen and thymus have not been 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).

2.2.2.4 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).

The epidemiological studies of the people exposed to trichloroethylene, as well as other chemicals, from well water in Wobum, Massachusetts, did not reveal neurological complaints (study limitations described in Section 2.2.2.8) (Byers et al. 1988; Lagakos et al. 1986a). Some of the people from this population did show 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). However, this study is limited by 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, POMS), 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 (Kilburn and Warshaw 1993). However, 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 exposure subregistry, a statistically significant increase in impairment of hearing was reported in children age 9 years or younger (ATSDR 1994; Burg et al. 1995). The relative risk in this group was 2.13 with a 95% confidence interval of 1.12-4.06. The study authors caution that their study does not identify a causal relationship between trichloroethylene and effects but does suggest areas for further research.

In animal studies, signs of neurotoxicity and neuropathology have been observed in response to oral doses of trichloroethylene. 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 gestation days 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 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). The rats were exposed to a dose of approximately 23.3 mg/kg/day.

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 (Bat-ret 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 2-2 and plotted in Figure 2-2.

2.2.2.5 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). In three communities in Michigan exposed to trichloroethylene and other solvents in drinking water, there was no increase in adverse pregnancy outcomes (Freni and Bloomer 1988).

A continuous breeding fertility study was conducted in which male and female Fischer-344 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 F_2 generation (NTP 1986). There was an increase in the relative left testis/epididymis weight in the F_0, generation and a decrease in absolute left testis/epididymis weight in the F_1 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-l 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 F_0 or F_1 mice, but sperm motility was reduced by 45% in F_0 males and 18% in F_1 males.

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.

Behavioral effects were noted when reproductive function was assessed in male Long-Evans rats that were given trichloroethylene in corn oil by gavage for 6 weeks (Zenick et al. 1984). Copulatory behavior was decreased at 1,000 ppm, and the study authors attributed this to the narcotic properties of trichloroethylene. Sperm count, motility, or morphology were not affected in these rats. The time between dosing and observation of copulatory behavior was not stated.

Histopathological changes in reproductive organs have not been 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 time-weighted average 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 2-2 and plotted in Figure 2-2.

2.2.2.6 Developmental Effects

There is some evidence that exposure to trichloroethylene in drinking water may cause certain types of birth defects. However, this body of research is still far from conclusive and there is insufficient evidence to determine whether or not there is an association between exposure to TCE and developmental effects. Two recent studies reported an association between exposure to TCE and neural tube defects and oral clefts. 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) found an association between trichloroethylene levels of >10 ppb and oral clefts, central nervous system defects, neural tube defects, and major cardiac defects (Bove et al. 1995). Uncertainty regarding exposure classification and small numbers of cases were the main limitations of this study. In a study of residents exposed to drinking water contaminated with solvents (including 267 ppb trichloroethylene) in Wobum, 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 2.2.2.8.

Additional studies of the Wobum population have been completed (MDPH 1994). The final report indicated that there was an increased prevalence in choanal atresia, a rare respiratory effect, and hypospadias/congenital chordee. A small increase in eye defects was observed, but there was no association between TCE exposure and heart defects. There was no statistically significant associations between exposure concentrations and birth defects, although analyses was limited by the small number of cases observed. Based on four cases in the Wobum population, a rate of 0.88 was observed in the exposed population, compared to rates of 0.11 and 0.13 in the Atlanta and California comparison populations, respectively. In a prospective study completed after well closure, the rate of choanal atresia was 0.88 (based on 1 case) in Wobum, 0.11 in the surrounding communities, and 0.2 and 0.13 in Atlanta and California, respectively. 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.

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 TCE contaminated water during the first trimester of pregnancy, the rate of congenital heart defects was approximately 2 l/2 times higher than among children of mothers who were not exposed to TCE 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. The mosi: significant limitation of this report is that the exposure was ill-defined. Exposures for individuals was not quantifiable, the areas that received TCE-contaminated water were not clearly delineated, the first year of exposure was unknown, the amount of TCE 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, although concentrations of TCE were highest.

Among persons in the ATSDR exposure subregistry, a statistically significant increase in impairment of hearing was reported in children age 9 years or younger (ATSDR 1994; Burg et al. 1995). The relative risk in this group was 2.13 with a 95% confidence interval of 1.12-4.06. Because the time of onset for hearing loss is not available, it is not known if this effect may be a result of *in utero* exposure or exposure after birth. The study authors caution that their study does not identify a causal relationship between trichloroethylene and effects but does suggest areas for further research.

Both Bove et al. (1995) and MDPH (1994) examined effects of trichloroethylene exposure on fetal birth weights. Neither study saw a conclusive effect on birth weight, although birth weights did tend to be lower in exposed infants compared to controls in the MDPH (1994) study. A small effect on birth weight in male infants was noted in preliminary findings in an interim report on adverse birth outcomes for a population (n=31) living at Camp LeJeune, North Carolina (ATSDR 1997). The women were exposed some time during gestation. The study authors cautioned that the small group size weakens the causal association. Further analyses are ongoing.

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, making statistically significant associations more difficult to identify.

Studies in animals indicate that trichloroethylene can act as a developmental toxicant, especially at doses also resulting 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 gestation days 6-19 in Fischer-344 rats (Narotsky and Kavlock 1995) or gestation days 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 l%, 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 (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 B6C3F_1mice treated by gavage with 240 mg/kg/day trichloroethylene in corn oil on gestation days l-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 F_1offspring of CD-l mice exposed to 750 mg/kg/day from conception through weaning (NIT 1986). Decreased maternal body weight gain and reduced fetal body weights were also observed, but there were no skeletal or visceral anomalies. Fischer-344 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).

In rats, 1,000 mg/kg/day trichloroethylene by gavage in corn oil increased several indicators of maternal toxicity and caused significant fetal mortality and decreased fetal body weight, but no significant teratogenic effects (Manson et al. 1984). Dawson et al. (1993) exposed groups of 9-39 female rats to trichloroethylene in drinking water (1.5 or 1,100 ppm) either before pregnancy (for 3 months prior to mating), before and during pregnancy (2 months prior plus 21 days into gestation), or during pregnancy only (21-day gestation). 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% in controls; 8.2% at 0.18 mg/kg/day; 9.2% at 132 mg/kg/day). This was based on examination of 2,037 hearts from litters of l-20 live fetuses (Johnson 1996). In dams exposed only during pregnancy, fetal heart defects were observed only at the higher dose (10.4% versus 3% in controls). While it is not known whether these effects were caused by trichloroethylene or its metabolites, the results provide qualitative support for human epidemiological studies that have found

higher incidences of congenital heart defects in children born to mothers exposed during pregnancy to trichloroethylene and dichloroethylene in drinking water (Goldberg et al. 1990). The study is limited in that only two widely spaced exposure concentrations were used and that a significant dose-response was not observed for several exposure scenarios.

Developmental neurotoxicity has been studied in very young animals exposed to trichloroethylene. 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 (Fredriksson et al. 1993). This study suggests that trichloroethylene affects brain maturation. Based on the 50-mg/kg/day LOAEL identified in the Fredriksson et al. (1993) study, an acute-duration oral MRL, of 0.2 mg/kg/day was calculated as described in the footnote in Table 2-2.

Open-field activity, a parameter in which hippocampal involvement has been implicated, was evaluated in 21- and 45-day-old F_1 rats that had been continuously exposed to trichloroethylene, *in utero* and throughout lactation via maternal dietary exposure (microcapsules), at doses ranging from approximately 75 to 300 mg/kg/day (NTP 1986). There was a significant dose-related trend toward an increase in the time required for grid traversal in the 21-day-old pups, but effects on other measures of open-field locomotor activity or miscellaneous behavior were not observed. Evaluation at 45 days was unremarkable, suggesting that trichloroethylene had a transient effect. Therefore, the 300-mg/kg/day dose is considered a NOAEL for this study. However, another series of studies has been completed in which female rats were exposed to trichloroethylene in drinking water for 14 days before mating, throughout gestation to weaning. Morphological (Isaacson and Taylor 1989), and functional neurological (Noland-Gerbec et al. 1986; Taylor et al. 1985) effects were assessed in the offspring. A 40% decrease in the number of myelinated fibers was observed in 21 -day-old offspring of rats provided with 312 mg/L trichloroethylene (about 37 mg/kg/day) (Isaacson and Taylor 1989). The magnitude of the effect was similar at the higher concentration (625 mg/L, 75 mg/kg/day). A decrease in myelinated fibers is considered a serious LOAEL. Glucose uptake by the brains 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 completed in 60-day-old rats showed increases in the offspring of rats provided with 312 mg/L trichloroethylene (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 2-2 and plotted in Figure 2-2.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans after oral exposure to trichloroethylene.

The data regarding the genotoxicity of trichloroethylene in animals are conflicting with both positive and negative results reported. One study reported that both male $B6C3F_1$ mice and Sprague-Dawley rats exhibited hepatic cell DNA damage in the form of single-strand breaks after oral exposure to trichloroethylene (Nelson and Bull 1988). The mice were much more sensitive to trichloroethylene than the rats; a single dose of 1.5 g/kg produced breaks in mouse DNA, compared to 3 g/kg in rats. Other groups of rats were pretreated 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 trichloroetbylene 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.

Other investigations using unscheduled DNA synthesis (UDS) assays reported that single gavage doses of trichloroethylene apparently caused no liver cell DNA damage in CD-1 mice (Doolittle et al. 1987), $B6C3F_1$ mice, or Fischer-344 rats (Mirsalis et al. 1989). Single doses of up to 1,000 mg/kg trichloroethylene did, on the other hand, cause an increase in the rate of DNA replication in both the CD-l mouse (Doohttle et al. 1987) and the $B6C3F_1$ mouse, but not in the Fischer-344 rat (Mirsalis et al. 1989). Increased DNA synthesis in hepatocytes and renal cells was observed in male but not female $B6C3F_1$ mice treated by gavage with 500 mg/kg/day trichloroethylene in corn oil for 7 days (Klaunig et al. 1991). In Fischer 344 rats treated by gavage with 500 mg/kg/day trichloroethylene in corn oil for up to 14 days, no effect on hepatocyte DNA

synthesis was observed, but renal DNA synthesis was increased in male but not female rats (Klaunig et al. 1991). Trichloroacetaldehyde (chloral), a major metabolite of trichloroethylene in humans and rodents, was tested for its ability to form hepatocyte DNA-protein cross-links *in vivo* in the $B6C3F_1$ mouse following oral doses of trichloroethylene. The results were negative (Keller and Heck 1988).

There is evidence that commercially available trichloroethylene may be weakly mutagenic to bacteria after metabolic activation (EPA 1985c), although the data are not conclusive. Concerning the mutagenicity of commercial trichloroethylene, it is probable that the responses were due to the presence of epoxide stabilizers, which are direct-acting mutagens. Data for purified samples were not conclusive, however, and a weak mutagenic effect was noted at high doses. Therefore, mutagenic potential for purified trichloroethylene cannot be disregarded; the data suggest that it could be a very weak indirect mutagen.

Other genotoxicity studies are discussed in Section 2.5.

2.2.2.8 Cancer

The link between oral exposure to trichloroethylene and the incidence of cancer in humans is controversial. Support for an association comes from a New Jersey study in which cancer registry data were correlated to data on drinking water contaminated with trichloroethylene (and other volatile organic hydrocarbon) (Fagliano et al. 1990). In this study, the standardized incidence ratio for leukemia was increased for females in towns with the highest exposure category (estimated volatile organic hydrocarbon levels ranged from 37 to 72 ppb). Shortcomings of this type of study include the lack of information on individual exposure levels, variations in the routes of exposure, and the presence of other volatile organic compounds. A subsequent study expanded the cohort size to about 1.5 million residents in 75 towns monitored between 1979 and 1987, and the results included a significant elevation of total leukemias, childhood leukemias, acute lymphatic leukemias, and non-Hodgkin's lymphoma in.groups of females exposed to >5.0 ppb trichloroethylene (Cohn et al. 1994). Diffuse large cell/reticulosarcoma non-Hodgkin's lymphoma was significantly elevated in males as well. In contrast, a survey of total cancer, liver cancer, non-Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma, and leukemia incidences from 1953 to 1991 in two Finnish villages with drinking water

contaminated with up to 220 ppb trichloroethylene and/or up to 180 ppb tetrachloroethylene found no significant increase in standardized incidence ratios for these diseases (Vartiainen et al. 1993).

Two investigations involving the review of mortality statistics for 1969-1979 concluded that there was a significantly elevated rate of childhood leukemia in Wobum, Massachusetts (Kotelchuck and Parker 1979; Parker and Rosen 1981). Two of the eight municipal wells servicing Woburn were known to be contaminated with trichloroethylene and several other chlorinated organic compounds, but etiologic factors for the leukemia were not identified in these studies. Two controversial studies found potential associations between ingestion of drinking water contaminated with solvents and increased risk of childhood leukemia, particularly acute lymphocytic leukemia (Byers et al. 1988; Lagakos et al. 1986a). Not all of the leukemia cases could be explained by the contaminated wells because several cases occurred in children with no access to these wells.

The studies performed at the Woburn site have several limitations (MacMahon 1986; Prentice 1986; Rogan 1986; Swan and Robins 1986; Whittemore 1986), including the presence of other contaminants and small sample size. One important difficulty is the poorly defined exposure conditions. The extent and duration of the contamination in the wells of concern are not known. Geophysical modeling has suggested that the contamination had probably been present earlier than the initial measurements that had identified the problem. This possibility makes the analyses of period-specific rates of effects incomplete since no time can be specified for the initiation of exposures. Two approaches were used in classifying exposures in the study by Lagakos et al. (1986a). The use of a continuous measurement based on estimates of the use and distribution of water from the contaminated wells actually showed less significance than the cruder measurement which grouped exposure into four categories. In addition, no attempt was made to account for water consumed from other sources, such as schools or workplaces. The contamination of the two wells at Woburn involved more than one measurable contaminant; thus, the adverse effects reported may not be attributable to trichloroethylene exposure alone.

A more recent study at Woburn was conducted by the Massachusetts Department of Health. Investigators found that the risk of leukemia in the group exposed to TCE in utero was about 8 times higher than that found in the unexposed group (MDPH 1996). It was concluded that these results were consistently in the direction of an association and support the hypothesis that childhood leukemia in this population may be

related to the mother's exposure to contaminated drinking water during pregnancy. Findings in this study are limited by the small numbers of cases and the limited information on exposures.

A study of three Michigan communities in which people were exposed to chlorinated solvents including trichloroethylene in drinking water showed no significant increases in cancers among the exposed population, including leukemia (Freni and Bloomer 1988). However, the cohort size in this study was only 223.

A health survey of 4,280 people exposed to trichloroethylene and other contaminants through drinking water in three states (Illinois, Indiana, and Michigan) has been completed (ATSDR 1994). An increase in respiratory tract cancers was observed in males. The study authors concluded that based on the incidence of smoking in the population "it would be inappropriate to relate this excess solely to trichloroethylene exposure."

Various types of cancers have been found in animals after trichloroethylene exposure by the oral route. There are problems, however, in interpreting the animal studies. Contamination of trichloroethylene with other potential carcinogens is one difficulty. For example, epoxides are often used to stabilize 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, $B6C3F_1$ 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 Fischer-344 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, this study has numerous limitations because of unusual reporting methods, such as failure to indicate the number of surviving animals and the absence of Good Laboratory Practices. 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.

In contrast to rats, $B6C3F_1$ mice developed hepatocellular carcinomas and hepatocellular adenomas following exposure to epoxide-free trichloroethylene (NTP 1990). The view of trichloroethylene as a hepatic carcinogen in mice but not rats was rienforced by a study in which rats were given trichloroethylene at 500 mg/kg/day by oil gavage for up to 14 days, 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.

Cancer effect levels (CELs) from all reliable studies are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.3 Dermal Exposure

2.2.3.1 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 more than 29 g/kg but did not report any other details (Smyth et al. 1969). No other dermal lethality dam were available.

2.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, renal, 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 riduals occupationally exposed to trichloth dermal and(Bauer and Rabens 1974; Phoon et al. 1984).

No studies were located regarding hepatic effects in animals after dermal exposure to trichloroethylene.

Dermal Effects. Because of the high volatility of trichloroethylene, human occupational exposure by dermal routes usually incudes 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, bums, 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 comeum (Goldsmith et al. 1988). The study indicates that lipid extraction is the reason for whitened skin following exposure to 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 three times a day for 3 days (Anderson et al. 1986).

2.2.3.3 Immunological and Lymphoreticular Effects

As discussed under dermal effects, people can develop hypersensitivity to trichloroethylene. The effects observed in hypersensitive individuals include skin effects (Conde-Salazar et al. 1983; Nakayama et al. 1988; Phoon et al. 1984; Waller et al. 1994) and liver effects (Phoon et al. 1984). Dermal sensitivity was confirmed with patch testing in only two cases (Conde-Salazar et al. 1983; Nakayama et al. 1988). The woman described by Conde-Salazaer et al. (1983) reacted positively to both vapor exposure and a dermal application of 5% trichloroethylene in olive oil.

No studies were located regarding immunological or lymphoreticular effects in animals following dermal exposure to trichloroethylene.

2.2.3.4 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; Kohhnuller and Kochen 1994).

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

No studies were located regarding the following health effects in humans or animals after dermal exposure to trichloroethylene:

2.2.3.5 Reproductive Effects

2.2.3.6 Developmental Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.3.8 Cancer

The combined incidence of stomach, liver, prostate, and lymphohematopoeitic cancers was increased among 2,050 male and 1,924 female Finnish workers occupationally exposed primarily to trichloroethylene (Antilla et al. 1995). The workers were exposed principally through 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 three times per 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.

2.3 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. Metabolism occurs fairly rapidly, and it may be that the resulting metabolites are responsible for much of the toxic effect 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 done for both animal and human systems (see Section 2.3.5), and predictions about target organ toxicity 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 2.4.3).

2.3.1 Absorption

2.3.1 .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 much 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 (Pernandez 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 (Mtiller 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 less than 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 mgkg 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).

2.3.1.2 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 (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 for clearance was found to be 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 mgkg in 50% aqueous polyethylene glycol400 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 from two to three 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 levels of up to 90% have been observed in rats dosed by this method (Prout et al. 1985).

Absorption kinetic studies on 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 have been due to trichloroethylene metabolites rather than the parent compound.

2.3.1.3 Dermal Exposure

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 a solution of unspecified trichloroethylene concentration for 30 minutes (Sato and Nakajima 1978). 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 comeum, 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 withnormal 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.

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 pure 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) increased rapidly, peaking at 0.5 hours (0.8 μg/rnL 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 in 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 liter of the water used for bathing. Thus, dermal absorption may be a significant route of human exposure to trichloroethylene from water-related sources.

Sex differences in uptake and metabolism of trichloroethylene have been seen in both humans and animals (see Section 2.8). 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). The mechanism behind this effect is still unclear.

2.3.2 Distribution

2.3.2.1 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; Mtiller et al. 1974). Once in the bloodstream, trichloroethylene may be transported rapidly to various tissues where it will likely be metabolized. Trichloroethylene was detected in the blood of babies at birth 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). Post-mortem analyses of human tissue from persons with unspecified exposure revealed detectable levels of trichloroethylene (< l-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.

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 may increase 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).

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.

2.3.2.2 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).

Limited data on tissue distribution following oral exposure in animals suggest that trichloroethylene is metabolized in the liver. Trichloroethylene that bypasses the liver is taken up by other tissues and sequestered in fat (Pfaffenberger et al. 1980). Rats were dosed by gavage with 1 or 10 mg/day trichloroethylene for 25 days, and blood serum and adipose tissue levels were determined at nine intervals during the exposure period and twice after cessation of dosing. Blood serum trichloroethylene levels were not detectable (i.e., <l µg /L serum) during the dosing period. Adipose tissue levels during the 25day exposure averaged 280 and 20,000 ng/g trichloroethylene for the l- and 10-mg/day doses, respectively. The average adipose trichloroethylene level was 1 ng/g for both exposure concentrations 3-6 days after the end of exposure.

2.3.2.3 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.

2.3.3 Metabolism

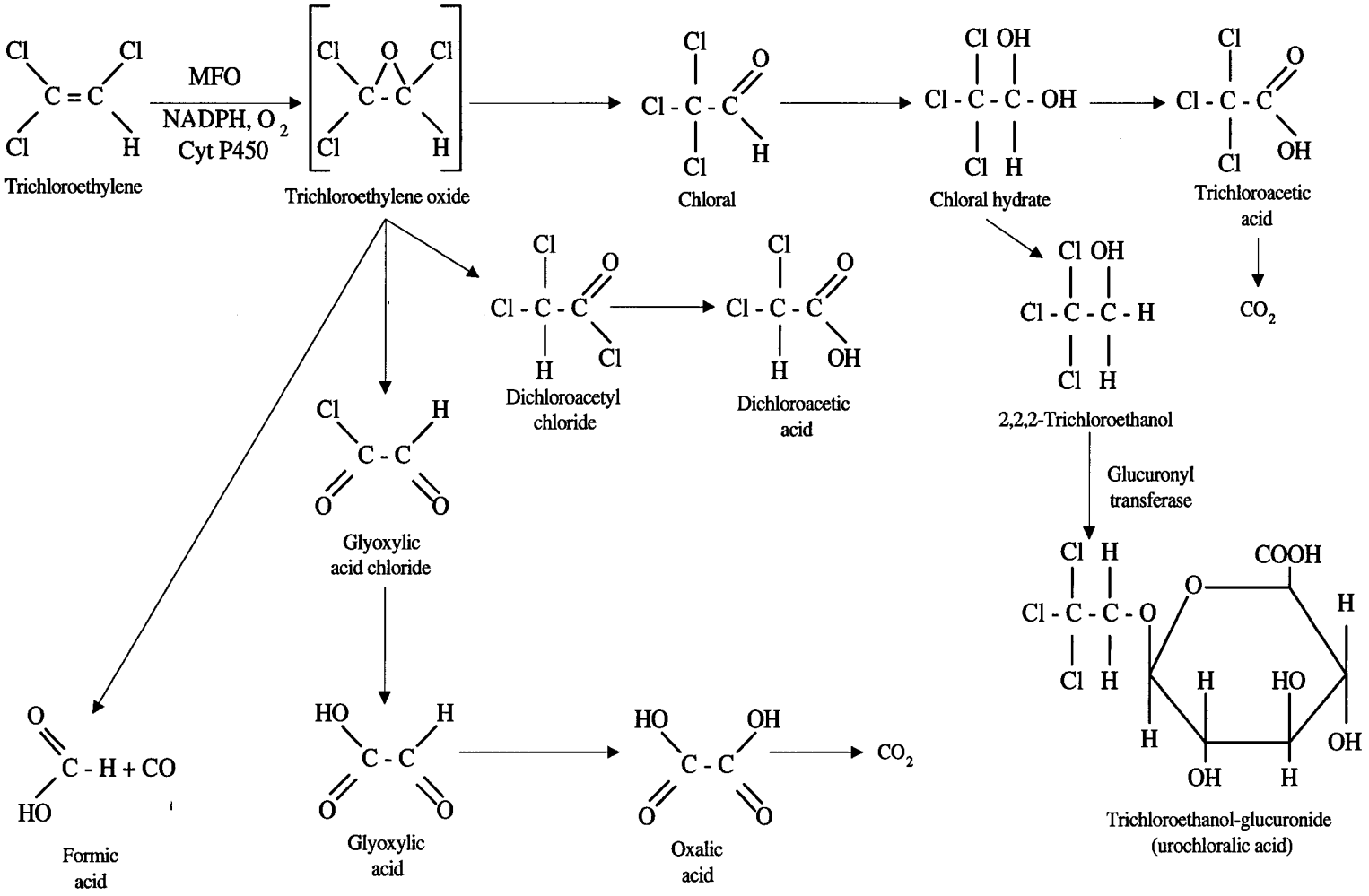
Inhaled doses of trichloroethylene are metabolized extensively in humans. The percentage of the dose metabolized has been reported to be between 40% and 75% of the retained dose (Bartonicek 1962; Ertle et al. 1972; Femandez et al. 1977; Kimmerle and Eben 1973a, 1973b; Monster et al. 1976, 1979; Mtiller 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. 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).

The principal metabolites of trichloroethylene in humans are trichloroethanol, trichloroethanol-glucuronide ("urochloralic acid"), and trichloroacetic acid (TCA) (Butler 1949; Cole et al. 1975; Mtiller 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). The major pathways of trichloroethylene metabolism in humans and animals are shown in Figure 2-3. Through an apparent epoxide intermediate, trichloroethylene oxide can form chloral, which rapidly converts to chloral hydrate. Chloral hydrate undergoes oxidation to TCA (Butler 1949). Alternatively, chloral hydrate can be metabolized to trichloroethanol, which undergoes Phase II glucuronidation to produce trichloroethanol-glucuronide (Miller and Guengerich 1983). Under certain conditions, the trichloroethylene-oxide intermediate can apparently form dichloroacetyl chloride and rearrange to dichloroacetic acid (DCA) (Dekant et al. 1984; Green and Prout 1985), or the oxide can hydrolyze to form formic acid, glyoxylic acid, oxalic acid, and carbon dioxide (Dekant et al. 1984; Green and Prout 1985). Minor urinary metabolites in trichloroethylene-exposed humans are monochloroacetic acid (Soucek and Vlachova 1960), N-(hydroxyacetyl)-aminoethanol, and DCA (Dekant et al. 1984).

The cytochrome P-450-dependent metabolism of trichloroethylene was studied in hepatic microsomal fractions from 23 different humans (Lipscomb et al. 1997). CYP2El was the predominant form of P-450 responsible for the metabolism of trichloroethylene in humans. Incubations of trichloroethylene with the microsomal preparations resulted in hyperbolic plots consistent with Michaelis-Menton 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/min/mg protein and were normally distributed. The study authors concluded that the human variability in metabolism of trichloroethylene via P-450-dependent pathways was within a 10-fold range.

FIGURE 2-3. The Metabolic Pathways of Trichloroethylene*



***Derived from Bogen et al. 1988**

Experiments demonstrate that oral absorption of trichloroethylene in animals is extensive and metabolism is rapid. A study of F344 rats which 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).

Urinary data in animals also show that the major metabolites of trichloroethylene are 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. It was also reported that chloroform is a minor metabolite of trichloroethylene (Mtiller et al. 1974; Pfaffenberger et al. 1980); however, this finding is questionable and needs further confirmation because chloroform may be an artifact of the analytical method used to identify metabolites. Other metabolites are the glutathione (GSH) conjugates of trichloroethylene and its metabolites (Miller and Guengerich 1983). GSH conjugation, although quantitatively not very important in trichloroethylene metabolism, may play an important role in the carcinogenicity/toxicity of trichloroethylene (see Section 2.4).

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 P-450 systems, evidence suggested the existence of a pre-epoxide transition state that involves the binding of

trichloroethylene to the activated oxygen of P-450, leading to chloral formation (Miller and Guengerich 1982, 1983).

Phenobarbital, an inducer of some forms of cytochrome P-450, has been shown to stimulate binding and metabolism of trichloroethylene by P-450 enzymes in rat liver microsome preparations (Costa et al. 1980). Similar stimulation of P-450-mediated trichloroethylene metabolism by phenobarbital has been demonstrated *in vivo* (Carlson 1974; Moslen et al. 1977). Using monoclonal antibodies against specific ethanol- and phenobarbital-induced P-450 enzymes in rat liver, Nakajima et al. (1992a) found that CYP2El was the most important isozyme involved in metabolizing trichloroethylene to chloral hydrate. The induction of these enzymes was also 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 CYP2El levels were lower in mature rats relative to immature rats. At puberty, the level of CYP2El 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 lo- and 600-ppm exposure concentrations, and there was no evidence of metabolic saturation. In rats, however, 98% of the net trichloroethylene uptake from the lo-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 high gavage doses of trichloroethylene, male mice metabolized trichloroethylene at a faster rate than male rats (Larson and Bull 1992b; Prout et al. 1985). The net metabolism of trichloroethylene to TCA and trichloroethanol was similar in rats and mice given single oral gavage doses of 1.5-23 mmol/kg (197-3,022 mg/kg) (Larson and Bull 1992b). However, 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 1992b). 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 1992b). This has been further validated by studies in which rats and mice had greater liver tumor induction with direct exposure to trichloroethylene metabolites such as DCA, TCA, chloral hydrate, or 2-chloroacetaldehyde (Bull et al. 1993; Daniel et al. 1992; DeAngelo et al. 1991; Larson and Bull 1992a).

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 &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. *In vitro* and *in vivo* data suggest that the cytochrome P-450 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). Isolated rabbit pulmonary cells (Clara, Type II, and alveolar macrophages) also demonstrated non-P-450-mediated bioactivation of trichloroethylene (Nichols et al. 1992). Trichloroethylene metabolism also appears to be important in trichloroethylene-induced nephrotoxicity (Dekant et al. 1986a; Elfarra and Anders 1984).

2.3.4 Elimination and Excretion

2.3.4.1 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). 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).

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 halftime 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 urinary excretion of TCA is much slower, and data from several studies indicate that the halftime of urinary TCA is approximately 52 hours because the metabolite is very tightly and extensively bound to plasma proteins (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 trichloro compounds and 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). In mice, 75% of the radioactivity was excreted in the

urine. Another 9% was exhaled as carbon dioxide. Rats excreted slightly less radioactivity in the urine and breath and more in the feces.

2.3.4.2 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.

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., less than 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 were given drinking water containing 4.8 ppm of [^{14}C]-trichloroethylene and that consumed 0.4 mg/kg 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).

2.3.4.3 Dermal Exposure

Elevated trichloroethylene levels in expired air were measured in subjects who immersed one hand in an unspecified concentration of trichloroethylene for 30 minutes (Sato and Nakajima 1978). Guinea pigs, exposed to dilute concentrations of aqueous trichloroethylene (≈ 0.020 to 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; 95% of the metabolized dose was excreted in 8.6 days (Bogen et al. 1992). No other studies were located for humans or animals regarding excretion after dermal exposure to trichloroethylene.

2.3.5 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). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic

behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

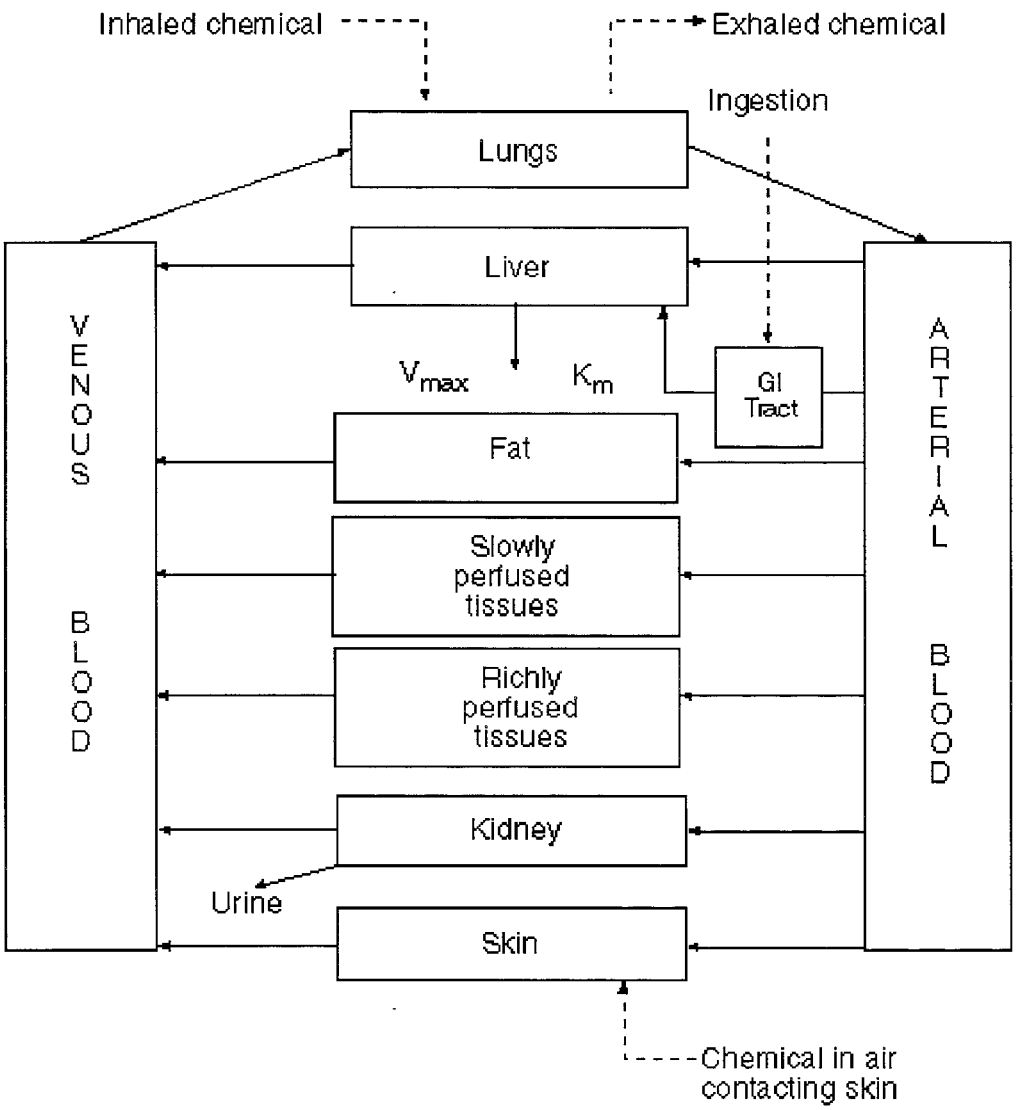
The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parameterization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s validated PBPK models were developed for a number of toxicologically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

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) is adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identity 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 2-4 shows a conceptualized representation of a PBPK model.

The overall results and individual PBPK models for trichloroethylene are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations. Several PBPK models have been developed for inhaled trichloroethylene. In au early model by Femandez et al. (1977), the human body was divided into three major compartments or tissue groups: the vessel-rich group (VRG), muscle group (MG), and adipose tissue (fat) group (FG). The distribution of trichloroethylene in these

Figure 2-4. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



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

compartments was predicted for an 8-hour inhalation exposure of 100 ppm. The model suggested that for short exposures to high concentrations, the absorbed dose will distribute to the VRG and be rapidly eliminated before significant accumulation in the MG and FG takes place. Although the model also predicted that the concentration of trichloroethylene in-the FG will increase very slowly even after the end of the exposure period, the FG was predicted to accumulate substantially higher concentrations of trichloroethylene than any other tissue in the body. Another model by Droz et al. (1989a, 1989b) expanded this model in an attempt to account for individual differences including body build, liver and renal function, exposure, and physical workload.

PBPK models have also been used to explain the rate of excretion of inhaled trichloroethylene and its major metabolites (Bogen 1988; Fisher et al. 1989, 1990, 1991; Ikeda et al. 1972; Ramsey and Anderson 1984; Sato et al. 1977). One model was based on the results of trichloroethylene inhalation studies using volunteers who inhaled 100 ppm trichloroethylene for 4 hours (Sato et al. 1977). The model used first-order kinetics to describe the major metabolic pathways for trichloroethylene in vessel-rich tissues (brain, liver, kidney), low perfused muscle tissue, and poorly perfused fat tissue and assumed that the compartments were at equilibrium. A value of 104 L/hour for whole-body metabolic clearance of trichloroethylene was predicted. Another PBPK model was developed to fit human metabolism data to urinary metabolites measured in chronically exposed workers (Bogen 1988). ‘This model assumed that pulmonary uptake is continuous, so that the alveolar concentration is in equilibrium with that in the blood and all tissue compartments, and was an expansion of a model developed to predict the behavior of styrene (another volatile organic compound) in four tissue groups (Ramsey and Andersen 1984).

Sato et al. (1991) expanded their earlier PBPK model to account for differences in body weight, body fat content, and sex and applied it to predicting the effect of these factors on trichloroethylene metabolism and excretion. Their model consisted of seven compartments (lung, vessel rich tissue, vessel poor tissue, muscle, fat tissue, gastrointestinal system, and hepatic system) and made various assumptions about the metabolic pathways considered. First-order Michaelis-Menten kinetics were assumed for simplicity, and the first metabolic product was assumed to be chloral hydrate, which was then converted to TCA and trichloroethanol. Further assumptions were that metabolism was limited to the hepatic compartment and that tissue and organ volumes were related to body weight. The metabolic parameters, V_{max} (the scaling constant for the maximum rate of metabolism) and K_m (the Michaelis constant), were those determined for trichloroethylene in a study by Koizumi (1989) and are presented in Table 2-3.

TABLE 2-3. Parameters Used in Two Human PBPK Models

Parameter	Sato et al. 1991	Fisher and Allen 1993
V_{max}	$10.2(BW)^{0.7}$	$14.9(BW)^{0.7}$
K_m	1.5	2.5
Alveolar ventilation (L/hour)	$17.8(BW)^{0.7}$	$12.6(BW)^{0.74}$
Cardiac output (L/hour)	$17.8(BW)^{0.7}$	$14.9(BW)^{0.74}$
Compartment		
Lung		
% Body weight	V_L[a]	-
% Cardiac output	100	-
Partition coefficient	-	-
Vessel rich		
% Body weight	3.0 (M), 3.0 (F)	-
% Cardiac output	37.9 (M), 37.9 (F)	-
Partition coefficient	3.4	-
Vessel poor		
% Body weight	8.5 (M), 8.5 (F)	-
% Cardiac output	6.3 (M), 6.3 (F)	-
Partition coefficient	1.6	-
Muscle		
% Body weight	41.5 (M), 31.5 (F)	-
% Cardiac output	11.4 (M), 8.7 (F)	-
Partition coefficient	1.6	-
Gastrointestinal		
% Body weight	1.9 (M), 1.9 (F)	-
% Cardiac output	17.1 (M), 17.1 (F)	-
Partition coefficient	2.8	-
Hepatic		
% Body weight	2.3 (M), 2.3 (F)	-
% Cardiac output	6.9 (M), 6.9 (F)	-
Partition coefficient	4.4	-
Arteriovenous shunt		
% Body weight	–	-
% Cardiac output	15.1 (M), 13.9 (F)	-
Partition coefficient	–	-
Fat		
% Body weight	21.1 (M), 36.5 (F)	19.0
% Cardiac output	5.3 (M), 9.2 (F)	5.0
Partition coefficient	68.0	73.3

TABLE 2-3 (*continued*)

Parameter	Sato et al. 1991	Fisher and Allen 1993
Liver		
% Body weight	–	2.6
% Cardiac output	–	26.0
Partition coefficient	–	6.8
Richly perfused		
% Body weight	–	5.0
% Cardiac output	–	44.0
Partition coefficient	–	6.8
Slow perfused		
% Body weight	–	62.0
% Cardiac output	–	25.0
Partition coefficient	–	2.4

[a]V_L = volume of lung compartment based on tidal volume, residual capacity, lung/air partition coefficient, and arterial blood volume

– = information not used in the model; BW = body weight (kg); F = female; M = male

This model accurately predicted the time curves for blood concentration and urinary excretion of metabolites by male volunteers exposed to 100 ppm trichloroethylene (Sato et al. 1991). It was found that, while the amount of metabolite excretion increases with body weight, the concentration does not, because of a corresponding increase in urinary volume. Also, women and obese people, compared with slim men, have lower concentrations but longer residence times of blood trichloroethylene because of their higher fat content (Sato et al. 1991). As a comequence, the model predicted that 16 hours after exposure to trichloroethylene, one could expect a woman's blood level to be 30% higher and an obese man's level to be twofold higher than that of a slim man (Sato 1993).

PBPK modeling has also been applied to the assessment of human cancer risk from trichloroethylene inhalation by considering the kinetics of its carcinogenic metabolite, TCA (Allen and Fisher 1993). This model was based on a previous model which explored trichloroethylene/TCA dynamics in rodents (Fisher et al. 1991). Four compartments were considered (rapidly perfused tissue, slowly perfused tissue, fat, and liver), and it was assumed that only the liver was involved in metabolism. Kinetic parameters were optimized by matching model predictions to results from published studies. Estimates obtained in this manner for TCA kinetics were as follows: the fraction of trichloroethylene metabolized to TCA was estimated as 0.33, the rate constant for elimination of TCA from the plasma was 0.028 h^{-1}, and the scaling constant for the TCA volume of distribution was found to be dependent on body weight (BW) and ranged from 0.34(BW) to 0.0034(BW) (Allen and Fisher 1993). The parameters used by the model for trichloroethylene metabolism (V_{max} and K_m) are presented in Table 2-3. The authors set the scaling constant for the trichloroethylene first-order metabolism rate at zero, citing a lack of evidence for a first-order pathway in humans (Allen and Fisher 1993).

A comparison of results indicated that the capacity for oxidation of trichloroethylene in humans is less than in $B6C3F_1$ mice but greater than in Fischer-344 rats (Allen and Fisher 1993; Fisher et al. 1991). In addition, the systemic concentration of TCA in mice was greater than in humans and rats. The increased body burden of TCA in mice may be related to the formation of hepatocellular carcinomas in mice exposed to trichloroethylene (Fisher et al. 1991); the significance of the predicted human body burden is as yet unclear. This model was also applied toward estimating liver and lung cancer risk from environmental exposure to trichloroethylene, using a linearized multistage model, and the results indicated that concentrations of

7.0 µg /L in water and 10.0 ppb in air each correspond to a cancer risk of 1 in 1 million (Fisher 1993; Fisher and Allen 1993).

Monte Carlo simulation, an iterative technique which derives a range of risk estimates, was incorporated into a trichloroethylene risk assessment using the PBPK model developed by Fisher and Allen (1993). The results of this study (Cronin et al. 1995), which used the kinetics of TCA production and trichloroethylene elimination as the dose metrics relevant to carcinogenic risk, indicated that concentrations of 0.09-l .0 µg /L, (men) and 0.29-5.3 µg /L (women) in drinking water correspond to a cancer risk in humans of 1 in 1 million. For inhalation exposure, a similar risk was obtained from intermittent exposure to 0.07-13.3 ppb (men) and 0.1643 ppb (women), or continuous exposure to 0.01-2.6 ppb (men) and 0.0343 ppb (women) (Cronin et al. 1995).

This study, like that of Fisher and Allen (1993), incorporated a linear multistage model. However, the mechanism of trichloroethylene carcinogenicity appears to be non-genotoxic, and a non-linear model (as opposed to the linearized multistage model) has been proposed for use along with PBPK modeling for cancer risk assessment. The use of this non-linear model has resulted in a 100-fold increase in the virtually safe lifetime exposure estimates (Clewell et al. 1995).

A PBPK model for acute and subchronic inhalation and drinking water exposures was developed for the kinetics of trichloroethylene and TCA in pregnant rats (Fisher et al. 1989) and in lactating rats and nursing pups (Fisher et al. 1990). Following maternal inhalation exposure to trichloroethylene, the parent compound and TCA were detected in both pregnant rats and the fetuses (Fisher et al. 1989,1990), whereas the metabolite was the major compound measured in nursing pups (Fisher et al. 1990). The PBPK model accurately predicted the time-course of these two compounds in the blood and the rate of metabolism of dams and pups following trichloroethylene inhalation or ingestion in drinking water (Fisher et al. 1990).

2.4 MECHANISMS OF ACTION

2.4.1 Pharmacokinetic Mechanisms

Absorption. Trichloroethylene, like other volatile hydrocarbons, causes generalized disruption of 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). Many observed neurotoxic effects of trichloroethylene have been attributed to demyelination resulting from such membrane disruption (Feldman et al. 1970, 1992). Experiments with muscle fibers have indicated that trichloroetbylene affects the dynamics of calcium ion transport across membranes (Kessler 1991), and a similar effect observed in cardiomyocytes has been offered as an explanation for trichloroethylene-induced cardiac arrhythmia (Hoffmann et al. 1994). Iron and trichloroethylene were found to synergistically promote lipid peroxidation in bovine pulmonary arterial endotbelial cells and rabbit aortic smooth muscle cells, suggesting a mechanism for the observed cardiac effects of trichloroethylene (Tse et al. 1990). Membrane interaction appears to be more pronounced at the interfacial region rather than the hydrocarbon core of the lipid bilayer (Bhakuni and Roy 1994). *In vitro* rabbit platelet activation, as measured by thrombin B, synthesis, was not inhibited by trichloroethylene, although inhibition by trichloroethanol was observed, thus implicating this metabolite in platelet membrane disruption (Yamazaki et al. 1992).

Distribution. Once inside the body, trichloroethylene is easily absorbed into and distributed through the circulatory system. The amount that is not absorbed initially on inhalation is expired unchanged (see Section 2.3.1.1). Absorption from the gastrointestinal tract often leads to a first pass through the liver, where toxic metabolites can form (see Section 2.3.3). Trichloroethylene and its metabolites may form adducts with blood proteins, and the metabolite glyoxylate may become incorporated into amino acids (Stevens et al. 1992), thus facilitating their distribution. The ability of these compounds to traverse membranes accounts for their generalized systemic effects.

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 (Femandez et al. 1977; Monster et al. 1979).

Excretion. Much of the initially inhaled trichloroethylene is expired unchanged, and trichloroethylene has been detected in the breath of people exposed orally and dermally as well. Once absorbed, trichloroethylene is rapidly metabolized by standard detoxification routes, such as the P-450 monooxidase and glutathione pathways, and many metabolic products are then excreted in the urine and feces. Differences among species in the primary metabolic pathways used may account for some differences seen in the toxic effect of trichloroethylene. For instance, high doses may saturate the P-450 pathway in rodents, causing a switch to glutathione conjugation, which may ultimately produce a metabolic product that is a renal carcinogen (Dekant et al. 1986a, 1986b; Miller and Guengerich 1982; Prout et al. 1985). However, no evidence exists for similar saturation in humans, which may partially account for the apparent absence of human renal cancer resulting from trichloroethylene exposure (Miller and%uengerich 1982; Steinberg and DeSesso 1993). No evidence exists for reabsorption, 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.

Effect of Dose and Duration of Exposure on Toxicity. Linearity of dose-response for trichloroethylene is often assumed, although this assumption has been challenged (Abelson 1993; Steinberg and DeSesso 1993). At low doses, the induction of detoxification pathways may be sufficient to minimize toxic effects, although saturation of these systems may occur at higher doses, potentially leading to the production of more toxic metabolites (see Section 2.3.3). Thus, a threshold effect may occur during chronic or high-dose exposure, leading to changes in the dose-response relationship.

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, and the liver, heart, and central nervous system are the primary targets for both routes (Candura and Faustman 199 l).- Renal toxicity results principally from oral exposure, and dermal exposure generally confines its toxic effects 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.

2.4.2 Mechanisms of Toxicity

Effects of Metabolism on Toxicity. Metabolism plays an important role in the toxicity of trichloroethylene because many of its metabolites are themselves toxic. Many differences among species in their responses to trichloroethylene exposure may be attributed to differences in the rates at which they metabolize the parent compound (Dekant et.al. 1986b; Prout et al. 1985).

An example is the rate by which the oxidative metabolism of trichloroethylene produces carcinogenic byproducts such as TCA. $B6C3F_1$ mice, which are far more prone to trichloroethylene-induced liver cancer, exhibit rapid metabolism of inhaled trichloroethylene, while F-34.4 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 its metabolites was greater in rats. 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).

Similarly, the metabolism of trichloroethylene to DCA, which may be important in the renal carcinogenic@ of trichloroethylene, appears to be a more commonly utilized pathway in rodents than in humans (Miller and Guengerich 1983; Steinberg and DeSesso 1993). The conjugation of DCA to GSH, followed by addition of L-cysteine, can eventually lead to the production of a reactive thiol group capable of binding to macromolecules (Dekant et al. 1986b). Several isomers of 1,2-dichlorovinyl-cysteine (DCVC), a product of trichloroethylene metabolism in the kidney, are mutagenic in the *in vitro* Ames assay (Commandeur et al. 1991; Dekant et al. 1986c). Production of of DCVC in humans is believed to occur by a minor pathway that is unlikely to become saturated and lead to kidney damage (Goeptar et al. 1995). However, N-acetylated

DCVC (a detoxification product of DCVC) has been identified in the urine of workers exposed to trichloroethylene (Bimer et al. 1993). 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, sexual differences due mainly to the effects of body fat content on trichloroethylene absorption are expected based on PBPK modeling (see Section 2.3.5).

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, heart, and kidneys. Central nervous system effects may also result in indirect toxic effects on heart, brain, and lung function. Retinal cell function appears to be targeted in rabbits at low exposures, based on electroretinogram changes following trichloroethylene injection (Blain et al. 1990) and visual evoked potential changes following trichloroethylene inhalation (Blain et al. 1992). Inhalation of trichloroethylene can produce toxic effects in rodent lungs, but the specific targeting of the lungs in exposed humans does not seem to be a major effect. Dermal contact with trichloroethylene can have effects on the skin as a result of defatting action and general irritation.

Species differences in the target organ specificity of trichloroethylene are exemplified by the case of the respiratory system. Mice exhibit greater susceptibility to trichloroethylene-induced lung tumors in chronic studies than do rats (Fukuda et al. 1983; Maltoni et al. 1986; NCI 1976), and short-term exposure studies have found that most cytotoxicity is specific to the Clara cells (Villaschi et al. 1991). Limited metabolism of trichloroethylene by cytochrome P-450 enzymes occurs in these cells, producing chloral (Miller and Guengerich 1983), a mutagen which may accumulate because of a limited ability of the cells to reduce it to trichloroethanol (Odum et al. 1992). Differences between rat and mouse pulmonary tumor induction may be thus attributed to differences in lung morphology: Clara cells are more abundant in mice and distributed in the bronchi and bronchioles, while those of the rat are located lower in the lung, where their exposure is reduced (Odum et al. 1992). The study authors further point out that, since trichloroethylene does not produce cancer in the rat lung and since Clara cell morphology of the rat lung is more similar to humans than mice, it is unlikely that the effect of trichloroethylene on the human lung would be like that of the mouse rather than like that of the rat. However, it is necessary to evaluate other potential mechanisms for lung toxicity and foci of activity that differ across species. When compared with national survey data, preliminary

data from the ATSDR Trichloroethylene Subregistry indicate an excess number of deaths from respiratory cancer in an older aged group exposed to TCE in the environment (ATSDR 1994). In addition, respiratory problems (including asthma and allergies) were moderately associated with cumulative TCE exposures. Although analyses of these data are ongoing, these findings suggest that adverse effects in the lung can occur in humans and may result from alternate mechanisms.

The liver is an organ that shows variable effects from trichloroethylene among species, and this can probably be attributed to interspecies differences in metabolism (see Section 2.4.2.1). Specifically, the apparent difference in susceptibility to trichloroethylene-induced hepatocelhtlar carcinoma between humans and rodents may be due to metabolic differences (see Section 2.4.2.3). Kidney effects are also variable among species. Humans and mice are less sensitive than rats. In rats exposed chronically to trichloroethylene, toxic nephrosis characterized as cytomegaly has been reported (NTP 1988). The kidney effects in rats do not seem to be related to an increase in alpha-2μ-globulin (Goldsworthy et al. 1988). Effects on the nervous system appear to be widespread among species, presumably due to interactions between trichloroethylene and neuronal membranes.

Carcinogenesis. The comparative carcinogenic potency of trichloroethylene and its metabolites, TCA and DCA, in the mouse liver was studied with the chemicals administered in drinking water (Herren-Freund et al. 1987). DCA and TCA, but not trichloroethylene, caused a significantly increased incidence of liver tumors with and without prior initiation with ethyhritrosourea. Although trichloroethylene was not shown to be a hepatocarcinogen in mice in this study, the amount of trichloroethylene that could be solubilized in the drinking water was quite low (40 mg/L) compared to DCA or TCA (5,000 mg/L). Other studies have shown that direct exposure to the trichloroethylene metabolites DCA, TCA, chloral hydrate, 2-chloroacetaldehyde) induces liver tumors, providing support to the theoretical mechanism of toxic metabolites in trichloroethylene-induced tumors in animals (Bull et al. 1993; Daniel et al. 1992; DeAngelo et al. 1991; Larson and Bull 1992a; Templin et al. 1993).

Hepatic peroxisome proliferation, characterized by liver enlargement due to hyperplasia and hypertrophy, has been proposed as a basis for differences in species susceptibility to trichloroethylene carcinogenicity. Peroxisomes are membrane-bound organelles which contain enzymes generally involved in lipid metabolism,

and their proliferation may be a response to perturbations in this metabolism (Bentley et al. 1993). Mechanisms by which peroxisome proliferation may induce cancer are unclear, although it has been speculated that the generation of increased levels of reactive oxygen species in peroxisomes may cause indirect DNA damage (Bentley et al. 1993). In addition, the general background of chronic cellular injury, necrosis, and regenerative cell growth common to peroxisome proliferation may result in sustained DNA synthesis, hyperplasia, and eventually cancer (Bentley et al. 1993; Steinberg and DeSesso 1993). Recent evidence of selective mutations in several codons of the H-ras oncogene in $B6C3F_1$ mice treated with trichloroethylene suggests this as a possible mechanism (but not the only one) of carcinogenicity as well (Anna et al. 1994).

Trichloroethylene exposure in male rats and .mice resulted in elevated cyanide-insensitive palmitoyl CoA oxidase levels, indicative of peroxisome proliferation (Goldsworthy and Popp 1987). In a similar experiment, exposure of mice and rats to high levels of trichloroethylene produced increased peroxisomal proliferation in mice but not rats (Elcombe et al. 1985). However, when mice and rats were exposed in the same study to the trichloroethylene metabolite TCA, both species responded with dramatic increases in peroxisome proliferation. Thus it seems that TCA is the agent of peroxisome proliferation induction, and differences among species in responses to trichloroethylene exposure may actually reflect differences in their metabolic pathways and hence their production of TCA. It is noteworthy that, at trichloroethylene dose levels that produce a strong peroxisomal proliferation response in rodents, no such effect is seen in humans (Bentley et al. 1993). Likewise, chronic dosing of trichloroethylene, while hepatocarcinogenic in mice, does not seem to be so in humans (N'TP 1990). However, Bull et al. (1993) caution that the metabolite DCA, also hepatocarcinogenic in mice. does not seem to act through peroxisome proliferation and thus may itself pose a risk for human cancer. More research needs to be done to resolve this issue.

Klaunig et al. (1991) found that hepatocyte DNA synthesis increased significantly in male mice exposed to trichloroethylene by gavage for up to 14 days, but no such increase was seen in female mice or in renal DNA synthesis in either sex. Similar exposures in rats produced increases in renal DNA synthesis in males, but no such increase in females, 01 .1n hepatic DNA synthesis in either sex. These results correlate well with observed species- and gender-specific trichloroethylene carcinogenicity, and the study authors suggest that trichloroethylene acts as a tumor promoter to induce proliferation of previously initiated cells.

Renal tubular cancer has been seen in rats following trichloroethylene exposure (NIP 1990). One possible explanation involves hyalin protein droplet induction associated with alpha-2_u-globulin accumulation in lysosomes, with cell proliferation in the P2 segment of the kidney, as seen when male rats are exposed to certain solvents (Goldsworthy et al. 1988). The increased cell proliferation associated with alpha-2_u-globulin, which is a male rat-specific protein (synthesized in the liver and excreted by the kidney glomemlus with reabsorption by the proximal convoluted tubular cell), may increase the possibility of spontaneous mutations, leading to tumor formation (Doolittle et al. 1987; Mirsalis et al. 1989). This histopathological alteration is not likely to be relevant for trichloroethylene toxicity in humans. However, for a number of chlorinated hydrocarbons, the development of renal tumors in male rats has been associated with alpha-2_u-globulin and hyaline droplet formation. In male Fischer-344 rats, no increase was noted in renal alpha-2_u-globulin concentration after exposure to trichloroethylene (Goldsworthy et al. 1988). Protein droplet accumulation and cell replication did not differ from controls in trichloroethylene-treated male or female rats (Goldsworthy et al. 1988).

Another possible mechanism for renal tumor development involves glutathione (GSH) conjugation of trichloroethylene and its metabolites; the quantitative significance of this route of metabolism is not clear, but it may play an important role when the oxidative P-450 pathway becomes saturated at high doses of trichloroethylene (Dekant et al. 1987). After administration of high doses of trichloroethylene, the conjugation product N-acetyl-dichlorovinyl-cysteine (DCVC) was found in the urine of the treated animals (Dekant et al. 1986a). Urinary dichlorovinyl-cysteine has also been identified in workers exposed to unspecified levels of trichloroethylene (Birner et al. 1993). It has been shown that cleavage of this conjugation product by β-lyase, an enzyme present in the renal tubule, leads to the formation of potentially nephrocarcinogenic metabolites (Dekant et al. 1986b).

Rats appear to be more sensitive to the nephrocarcinogenic effects of trichloroethylene (NTP 1990). This may be due to pathways other than glutathione conjugation and subsequent β-lyase cleavage,since the extent of trichloroethylene activation through this pathway, as measured by production of acid-labile adducts to renal proteins, was greater ir, mice than in rats (Eyre et al. 1995a). The amount of DCVC found in rat kidneys after oral exposure to trichloroethylene was four to six times greater than that found in mouse kidneys after an equivalent exposure, suggesting more efficient glutathione conjugation, and subsequent

DCVC formation, in rats (Eyre et al. 1995b). However, this study also found renal activation of DCVC to nephrocarcinogenic byproducts in mice to be 12 times greater than in rats, resulting in the overall renal activation of trichloroethylene by the cysteine S-conjugate pathway in mice being double that of rats. Agents which inhibit P-lyase protect against DCVC nephrotoxicity in rats (Elfarra et al. 1986). Additional insight into the role of dichlorovinyl-cysteine in nephrocarcinogenicity was provided by McLaren et al. (1994), who noted that it induces DNA double-strand breaks and poly(ADP-ribosyl)ation (a post-translational modification which affects DNA repair enzymes) in the rat renal cortex.

2.4.3 Animal-to-Human Extrapolations

Extrapolating animal toxicity data to predict human risk is often controversial and is especially so in the case of trichloroethylene since some of the mechanisms implicated in its animal effects do not apparently exist in humans. For instance, trichloroethylene-induced peroxisome proliferation, a potential precursor to hepatocarcinoma induction, is common in rodents but not in humans (Bentley et al. 1993; Elcombe 1985). Abelson (1993) has pointed out that, while the metabolism of trichloroethylene to TCA is rapid and linear in mice, leading to peroxisome proliferation and carcinogenesis, the same metabolic pathway in rats and humans is limited, as is the evidence for peroxisome proliferation and carcinogenesis. However, the metabolite DCA is also hepatocarcinogenic in mice, though it is not an effective peroxisome proliferator, so the implications for human hepatocarcinogenicity are still unclear (Bull et al. 1993). Differences in lung morphology among rodents and humans may help explain species differences in susceptibility to respiratory tumors resulting from trichloroethylene inhalation (see Section 2.4.2.2).

On the other hand, chloral, a metabolite of trichloroethylene, which is also a mutagen and inducer of aneuploidy, is produced via a pathway which is more predominant in rats and humans than in mice (Kimbrough et al. 1985). A study using identical trichloroethylene concentrations in rats and mice, and which found increased aneuploidy in rats but no effect in mice, offered this mechanism as a possibleexplanation (Khgerman et al. 1994). An implication from this would be that humans are similarly more susceptible to chloral-mediated effects of trichloroethylene exposure.

It thus appears that, as models for predicting human susceptibility to trichloroethylene-induced cancer, mice may be less than satisfactory, while rats may be slightly better. Much of the available epidemiological evidence for exposed humans does not seem to indicate that trichloroethylene is a prominent carcinogen at concentrations usually found at worksites or in the environment (Abelson 1993). However, the database also includes limited evidence that suggests carcinogenic effects, such as leukemias, may be linked to trichloroethylene exposure (Fagliano et al. 1990; Lagakos et al. 1986a). These studies are limited by exposure to multiple chemicals.

Developmental effects of trichloroethylene exposure have been demonstrated with the FETAX (Frog Embryo Teratogenesis Assay Xenopus) bioassay, an *in vitro* method using whole frog embryos (Fort et al. 1991, 1993; Raybum et al. 1991). Observed defects included gut m&coiling, skeletal kinking, and heart malformations; heart malformations have also been observed in rat developmental assays (Dawson et al. 1993).

2.5 RELEVANCE TO PUBLIC HEALTH

Exposure to trichloroethylene can occur via the inhalation, oral, and dermal routes in people living in areas surrounding hazardous waste sites if evaporation occurs from contaminated soils or spill sites, or if contaminated water is ingested or used in bathing. Individuals who work in the vicinity of industries that use this substance may breathe trichloroethylene vapors or come into physical contact with spilled trichloroethylene. The group with the greatest likelihood for substantial exposure to trichloroethylene consists of those exposed to trichloroethylene in the workplace.

In the past, trichloroethylene was used as a human anesthetic. Trichloroethylene has also been used by individuals who intentionally inhale it for its narcotic properties. Therefore, most of the information regarding the effects of trichloroethylene in humans comes from case studies and experiments describing effects of trichloroethylene after inhalation exposure. These studies indicate that the primary effect of exposure to trichloroethylene is on the central nervous system. Effects include headache, vertigo, fatigue, short-term memory loss, decreased word associations, central nervous system depression, and anesthesia.

Minimal Risk Levels for Trichloroethylene

Inhulution MRLs

- An MRL of 2 ppm was derived for acute inhalation exposure (14 days or less) to trichloroethylene. This MRL was based on a study by Stewart et al. (1970) in which volunteers were exposed to 200 ppm trichloroethylene for 5 days, 7 hours/day. A LOAEL was observed for mild subjective neurological effects, such as fatigue and drowsiness. Support for this end point is provided by human case studies of cardiac arrhythmia after unspecified trichloroethylene exposure (Dhuner et al. 1957; Milby 1968; Thierstein et al. 1960), and by decreased wakefulness and post-exposure heart rate in rats exposed to 1,000 ppm (Arito et al. 1993). Kishi et al. (1993) observed decreased shock avoidance and Skinner box lever press in rats after exposure to 250 ppm trichloroethylene, although performance was variable among individuals. Other human studies, while not acceptable for MRL derivation because of shortcomings in experimental design, nevertheless reported decreased reaction time at 110 ppm after 8 hours (Salvini et al. 1971); studies involving exposures of 300 ppm or less for fewer than 4 hours found no effects in several neurological tests (Ettema et al. 1975; Konietzko et al. 1975a; Windemuller and Ettema 1978). These studies generally support the LOAEL of 200 ppm used for the MRL derivation.

- An MRL of 0.1 ppm was derived for intermediate inhalation exposure (15-364 days) to trichloroethylene. This MRL was based on a study by Arito et al. (1994a) in which male JCL-Wistar rats were exposed to 0, 50, 100, or 300 ppm trichloroethylene for 6 weeks, 5 days/week, 8 hours/day. A LOAEL of 50 ppm was observed for decreased wakefulness during exposure, and decreased post-exposure heart rate and slow wave sleep. Another study with rats found an increase in sleep-apneic episodes and cardiac arrhythmias after exposure to trichloroethylene (Arito et al. 1993). These results corroborate similar effects observed in humans exposed to trichloroethylene, as described in the previous paragraph, as well as evidence of organic solvent-induced sleep apnea in humans (Edling et al. 1993; Monstad et al. 1987, 1992; Wise et al. 1983).

No chronic inhalation exposure (365 or more days) MRL was derived for trichloroethylene because the available chronic-duration data were limited by lack of adequate characterization of exposure conditions or quantitation of results, or because the existing studies had end points that were not suitable for derivation of anMRL.

Oral MRLs

- An MRL of 0.2 mg/kg/day was derived for acute oral exposure (14 days or less) to trichloroethylene. This MRL was based on the study by Fredriksson et al. (1993) in which mouse pups were dosed by gavage with 0, 50, or 290 mg/kg/day trichloroethylene in a 20% peanut oil emulsion between the ages of 10 and 16 days. Behavioral changes (reduced rearing rate) were noted during tests performed at

60 days of age. Support for this developmental end point was provided by similar studies involving dose-related but transient changes in open field behavior (NT.P 1986) and changes in exploratory behavior (Taylor et al. 1985) in rat pups from dams exposed to trichloroethylene during gestation, as well as reports of decreased myelination of brain neurons (Isaacson and Taylor 1989) and decreased uptake of 2-deoxy-D-glucose in the brain (Noland-Gerbec et al. 1986) in rat pups from exposed dams.

No intermediate oral exposure MRL was derived for trichloroethylene because of a lack of adequately designed studies examining suitable end points. No chronic oral exposure MRL was derived for trichloroethylene because the existing studies had end points that were not suitable for derivation of an MRL.

Death. Humans have died after breathing (Bell 1951; Buxton and Hayward 1967; Clearfield 1970; DeFalque 1961; Ford et al. 1995; James 1963; Kleinfeld and Tabershaw 1954; McCarthy and Jones 1983; Smith 1966; Troutman 1988) or drinking (Kleinfeld and Tabershaw 1954; Secchi et al. 1968) very large amounts of trichloroethylene. This occurred during acute accidental workplace atmospheric exposures, or by intentional ingestion or inhalation of large doses of the substance in order to commit suicide or become intoxicated. The deaths following acute inhalation exposure were generally attributed to ventricular fibrillation or central nervous system depression, while the deaths following acute oral exposure were attributed to hepatorenal failure. Death associated with liver failure has 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). Reports regarding the death of humans following dermal exposure to trichloroethylene were not located.

Animals have also died following large inhalation (Kylin et al. 1962; Siegel et al. 1971) or oral exposures (Merrick et al. 1989; Smyth et al. 1969; Tucker et al. 1982). Deaths in animals have also been reported following chronic-duration inhalation exposure (Henschler et al. 1980) and following intermediate- and chronic-duration oral exposure (Henschler et al. 1984; NCI 1976; NTP 1990). No deaths due to dermal exposure have been reported. Death is not likely to result from exposure to low levels of trichloroethylene at hazardous waste sites.

Systemic Effects

Respiratory Effects. Labored breathing and respiratory edema were reported in a worker after welding steel that had been washed with trichloroethylene (Sjogren et al. 1991). These effects may be a result of the trichloroethylene decomposition products phosgene and dichloroacetyl acid.

Some members of a community that were exposed to trichloroethylene along with a variety of other solvents in their drinking water complained of respiratory disorders, but the complaints could not be attributed specifically to trichloroethylene (Byers et al. 1988). This effect may have been due to imrnune system impairment resulting in increased susceptibility to infection. A study in mice in which inhalation exposure to trichloroethylene increased the susceptibility to pulmonary infection with *Streptococcus zooepidemicus* (Aranyi et al. 1986) provides evidence that trichloroethylene may result in adverse respiratory effects through effects on the immune system.

Vacuole formation and endoplasmic reticulum dilation in the Clara cells have been observed in mice (Odum et al. 1992; Vilaschi et al. 1991) but not rats (Odum et al. 1992) exposed to trichloroethylene by inhalation. The increased sensitivity of mice to this effect is thought to result from the greater abundance of these cells in mice and the difference in the distribution of these cells in mice compared to rats (Odum et al. 1992). Rales and dyspnea have been reported in pregnant rats treated by gavage with high doses of trichloroethylene (Narotsky and Kavlock 1995). Following intermediate-duration oral exposure to high doses of trichloroethylene, pulmonary vasculitis has been reported in rats (NTP 1990). Although exposure to trichloroethylene at levels found in the environment or at hazardous waste sites is unlikely to result in direct respiratory effects, the data suggest that increased susceptibility to respiratory infection secondary to immune system effects may occur.

Cardiovascular Effects. Chronic cardiovascular disease has not been reported in workers occupationally exposed to low levels of trichloroethylene (El Ghawabi et al. 1973), although deaths following acute highlevel 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 (Bell 1951; Kleinfeld and Tabershaw 1954; Smith 1966), poisoning (Dhuner et al. 1957; Gutch et al. 1965), or

anesthesia (Pembleton 1974; Thierstein et al. 1960). Accidental oral exposure to trichloroethylene has resulted in cardiac arrymmias (Dhuner et al. 1957; Morreale 1976; Perbellini et al. 1991). Cardiac arrhythmias reported in a small number of people who drank from contaminated wells could not be attributed to trichloroethylene alone (Byers at al. 1988). 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 (Goldberg et al. 1990). When compared with a national sample, the ATSDR subregistry of persons environmentally exposed to trichloroethylene reports excesses of anemia, stroke, blood disorders, and death from heart disease (ATSDR 1994; Burg et al. 1995). However, the data were gathered by questionnaire and may be limited by self-reporting bias.

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 this agent (Morris et al. 1953; Reinhardt et al. 1971; White and Carlson 1979,1981). Cardiac arrhythmias were reported in rats exposed to trichloroethylene (Arito et al. 1993), and an intermediate-duration inhalation exposure MRL of 0.1 ppm was derived from another study in which this effect was found in rats (Arito et al. 1994a). Exposure to trichlc roethylene has been correlated with cardiac abnormalities in developing chick embryos (Loeber et al. 1988) as well as rat fetuses (Dawson et al. 1990). Histopathological changes in the heart have not been observed in animals exposed to trichlorethylene following intermediate-duration exposure periods (Prendergast et al. 1967; Reinhardt et al. 1973; White and Carlson 1979,1981,1982). 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 (Okamoto and Shiwaku 1994). The evidence is suggestive that cardiovascular effects could be a concern for persons exposed to trichloroethylene near hazardous waste sites.

Gastrointestinal Effects. Case reports indicate that acute inhalation exposure to trichloroethylene results in nausea and vomiting (Buxton and Hayward 1967; Clear-field 1970; David et al. 1989; DeFalque 1961; Gutch et al. 1965; Milby 1968). Anorexia, nausea, vomiting, and intolerance to fatty foods have also been reported after chronic occupational exposure to trichloroethylene (El Ghawabi et al. 1973; Schattner and Mahrick 1990; Smith 1966). Trichlcroethylene-induced effects on the autonomic nervous system may contribute to these effects (Grandjean et al. 1955). Some of the people exposed to trichloroethylene and other chlorinated

hydrocarbons in the drinking water in Woburn, Massachusetts, occasionally complained of chronic nausea, episodic diarrhea, and constipation (Byers et al. 1988). Pneumatosis cystoides intestinalis has been described in workers exposed by inhalation to >50 ppm trichloroethylene as well as other solvents (Nakajima et al. 1990a). Self-reported gastrointestinal problems were not increased among persons in the trichloroethylene subregistry who were exposed to trichloroethylene in their drinking water (ATSDR 1994; Burg et al. 1995).

In a chronic inhalation study, histological changes in the gastrointestinal tract were not observed in rats (Maltoni et al. 1988). Gas pockets in the intestinal coating and blood in the intestines were observed in mice treated with trichloroethylene in drinking water (Tucker et al. 1982). The effect was not dose-related, and statistical analysis was not reported. Histopathological changes in the gastrointestinal tract have not 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).

Based on the limited human and animal data, it is not possible to predict whether or not trichloroethylene exposure at levels found in the environment and at hazardous waste sites can result in gastrointestinal effects.

Hematological Effects. The limited number of studies of humans exposed to trichloroethylene for an acute period (7 hours/day for 1 or 5 days) revealed no adverse effects on blood cell counts, sedimentation rates, serum lipid levels, serum proteins, or serum enzymes (Stewart et al. 1970). Blood cell counts were not affected in volunteers exposed to trichloroethylene for 2 hours (Vernon and Ferguson 1969). Volunteers inhaling 95 ppm trichloroethylene for 4 hours showed only an increase in neutrophil enzyme levels, with no change in serum enzyme levels (Konietzko and Reilll980). Effects on hemoglobin levels or red blood cell counts were not observed in persons occupationally exposed to trichloroethylene (Konietzko and Reilll980). Hematological effects have not been reported in cases of accidental oral exposure to trichloroethylene (perbellini et al. 1991; Todd 1954). The trichloroethylene subregistry, which has compiled information on 4,280 people exposed to trichloroethylene through their drinking water, found a significantly increased incidence of anemia among selected age groups when compared with corresponding national data (ATSDR 1994; Burg et al. 1995).

Changes in hematology end points were not observed in rats following intermediate-duration inhalation exposures to trichloroethylene (Prendergast et al. 1967). 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 (Pujita et al. 1984; Koizumi et al. 1984). Related effects included increased ALA synthetase activity and reduced heme saturation of tryptophan pyrrolase in the liver, increased urinary excretion of ALA and coproporphyrin, and reduced cytochrome P-450 levels in me liver. Hemoglobin concentration in erythrocytes did not change, and 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). Oral ingestion of trichloroethylene in drinking water for 6 months resulted in minor hematological changes in mice, 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). The effects were not dose related, and some effects were transient. Although available evidence suggests only minor hematological effects in humans, animal studies show hematological effects. Thus, hematological effects in humans exposed to environmental levels of trichloroethylene from hazardous waste sites may be a concern.

Musculoskeletal Effects. No studies were located regarding direct musculoskeletal effects in humans following any route of exposure. Trichloroethylene can result in nervous system effects that result in secondary effects on muscle strength, especially in the face (Leandri et al. 1995).

Histopathological changes in muscles have not been observed in rats following chronic-duration inhalation exposure to trichloroethylene (Maltoni et al. 1988), or in rats or mice following intermediate-duration or chronic-duration oral exposure to trichloroethylene (Maltoni et al. 1986; NCI 1976; NTP 1988, 1990). Histopathological changes in bone have also not been observed in rats or mice following oral exposure to trichloroethylene (NTP 1988, 1990). Based on the available data, direct musculoskeletal effects are unlikely in humans following exposure to trichloroethylene at levels found in the environment, or at hazardous waste sites. Effects on muscle strength secondary to neurological effects may be a concern.

Heputie Effects. There is some evidence for trichloroethylene-induced hepatic effects in humans. This evidence is primarily from case reports of persons accidently or intentionally exposed to relatively high levels.

Hepatic necrosis has been observed in persons that died following inhalation (Joron et al. 1955; Priest and Horn 1965) or oral (Kleinfeld and Tabershaw 1954) exposure to high levels of trichloroethylene. Although death resulting from hepatic failure in eclamptic pregnant women has been reported following trichlorethylene anesthesia (DeFalque 1961), controlled trichloroethylene anesthesia generally produces minimal effects on the liver indicated by increased serum levels of SGGT (Pembleton 1974). Other studies of humans following trichloroethylene anesthesia have not reported adverse effects (Brittain 1948; Crawford and Davies 1975). A significant increase in the metabolism of the drug paracetamol was observed in patients anesthetized with trichloroethylene, indicating subtle effects on liver function may make determining the proper dosage more difficult (Ray et al. 1993). Liver effects were not reported in acute-duration human exposure studies (Konietzko and Reill 1980; Stewart et al. 1970).

Liver effects including blood and urine indices of liver function, and enlarged livers, have been reported in persons occupationally exposed to trichloroethylene (Bauer and Rabens 1974; Capellini and Grisler 1958; Graovac-Leposavic et al. 1964; Phoon et al. 1984; Schattner and Malnick 1990; Schuttmann 1970). Exposure concentrations in these studies were not reported. In contrast no evidence of hepatoxicity was observed in workers who had neurological effects from trichloroethylene (McCarthy and Jones 1983).

Several cases of accidental oral exposure to trichloroethylene have not reported hepatic effects (Morreale 1976; Perbellini et al. 1991; Todd 1954). Self-reported liver problems were not increased among persons in the ATSDR trichloroethylene subregistry who were exposed to trichloroethylene in their drinking water (ATSDR 1994; Burg et al. 1995).

Liver enlargement is the primary hepatic effect seen in trichloroethylene-exposed animals after oral or inhalation exposure, indicating that trichloroethylene is not as potent a liver toxin as are a number of other chlorinated hydrocarbons. However, many of the studies were limited by lack or inadequate scope of pathological examinations, lack of measurement of hepatic enzymes, and/or failure to evaluate liver function indices. Histological alterations characterized by cellular hypertrophy were associated with liver enlargement in some of the studies of mice exposed to trichloroethylene in the air (Kjellstrand et al. 1981,1983a, 1983b) or via the oral route (Buben and O'Flaherty 1985; Elcombe 1985; Goldsworthy and Popp 1987; Stott et al.

1982; Tucker et al. 1982). Increasing severity of liver necrosis with dose was also seen in the studies by Buben and O'Flaherty (1985) and Stott et al. (1982).

Increased liver weight and hypertrophy may be due to the induction of peroxisomal P-oxidation. Mice, especially males, appear to be particularly sensitive to the hepatic effects of trichloroethylene (Kjellstrand et al. 1983b). Differences in the hepatic effects of trichloroethylene between mice, rats, and humans are attributable to the greater metabolism of high doses of trichloroethylene by mice compared to rats and humans (Dekant et al. 1986b; Larson and Bull 1992b; Stott et al. 1982), as well as a much greater induction in peroxisomes following exposure to trichloroacetic acid (Bentley et al. 1993). A study in male mice showed increased liver weight at a dose of 100 mg/kg/day trichloroethylene and enlarged hepatocytes at 400 mg/kg/day (Buben and O'Flaherty 1985). Histopathological changes of the liver (including necrosis) were seen at higher doses. Although there are conflicting reports in humans and limitations in animal studies, these data together suggest that hepatic effects may be a concern for some persons exposed to trichloroethylene; however, it is unknown whether exposure to levels of trichloroethylene found in and around hazardous waste sites may result in hepatic injury.

Renal Effects. People who have been acutely exposed to high vapor levels during surgical anesthesia (Brittain 1948; Crawford and Davies 1975) have not exhibited renal toxicity. However, minor changes in urinary and serum indicators of renal function have been found in some workers occupationally exposed to trichloroethylene (Brogren et al. 1986; Clearfield 1970; David et al. 1989; Gulch et al. 1965; Nagaya et al. 1989b; Selden et al. 1993). Acute accidental oral exposure to trichloroethylene has not resulted in effects on renal function (Morreale 1976; Perbellini et al. 1991; Todd 1954). 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 (Freni and Bloomer 1988; Lagakos et al. 1986a).

Acute inhalation exposure of rats to high concentrations of trichloroethylene has resulted in increases in urinary glucose, proteins, glucosaminidase, gamma glutamyl transpeptidase, and serum urea nitrogen (Chakrabarti and Tcuhweber 1988). Following intermediate-duration inhalation exposure of animals to trichloroethylene, increased kidney weights have been observed (Adams et al. 1951; Kimmerle and Eben 1973a; Kjellstrand et al. 1981, 1983a, 1983b; Prendergast et al. 1967). Chronic-duration inhalation exposure

of rats to trichloroethylene has resulted in renal tubular meganucleocytosis in males but not females (Maltoni et al. 1986,1988). With the exception of mild to moderate cytomegaly and karyomegaly in the renal tubular epithelial cells observed in an intermediate-duration oral study in mice (NTP 1990), acute- and intermediate-duration oral studies of trichloroethylene in mice have not reported significant renal effects (Goldsworthy et al. 1988; Stott et al. 1982; Tucker et al. 1982). Rats are more sensitive to the renal effects of trichloroethylene than mice. Following intermediate-duration oral exposure, the effects noted included increased kidney weights, elevated urinary protein and ketones (Tucker et al. 1982), minimal to mild cytomegaly, and karyomegaly of the renal tubular epithelial cells (NTP 1990). Treatment-related chronic nephropathy has been observed in rats (Maltoni et al. 1986; NCI 1976; NTP 1988, 1990) and mice (NCI 1976) following chronic oral exposure to trichloroethylene. Although there are few data in humans and limitations in animal studies, the data suggest that kidney effects may be a concern for some persons exposed to trichloroethylene; however, it is unknown whether exposure to levels of trichloroethylene found in and around hazardous waste sites may result in renal injury.

Endocrine Effects. No studies were located regarding endocrine effects in humans following any route of exposure. Adrenal gland weight was not affected following acute-duration oral exposure of rats to trichloroethylene (Berman et al. 1995). Histopathological changes have not been reported in endocrine glands following inhalation (Maltoni et al. 1988) or oral (Maltoni et al. 1986; NCI 1976; NTP 1988,1990) exposure to trichloroethylene for intermediate- or chronic-durations. Based on the limited data, histopathological changes are unlikely in humans exposed to trichloroethylene at levels found in the environment or at hazardous waste sites. The data are not sufficient to predict if subtle changes in endocrine gland function may occur in humans exposed to trichloroethylene at levels found in the environment or at hazardous waste sites.

Dermal Effects. Some humans experienced dry throats following acute inhalation exposure to trichloroethylene at 200 ppm (Stewart et al. 1970). Persons working with trichloroethylene for intermediate periods sometimes develop skin rashes and dermatitis (Bauer and Rabens 1974; El Ghawabi et al. 1973). It is reported that some people may be particularly sensitive to trichloroethylene and develop allergies when exposed to high levels in the air or on their skin during occupational exposures of intermediate duration (Czirjak et al. 1993; Goh and Ng 1988; Nakayama et al. 1988; Phoon et al. 1984). Exposure to

trichloroethylene and other substances in drinking water has been associated with an increase in maculopapular rashes (Byers et al. 1988). Diffuse fascitis has been reported in a woman, but not her husband, although both were exposed to trichloroethylene and other chlorinated hydrocarbons in well water (Wailer et al. 1994). Substitution of bottled water for drinking resulted in improved symptoms. Dermal effects of trichloroethylene are usually the result of direct skin contact with trichloroethylene, which results in desiccation due to the defatting action of the solvent. It is also possible that adverse dermatological effects may be mediated by immunological responses in some persons.

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 for intermediate durations (NCI 1976). Histopathological changes in the skin were not observed in rats following chronic inhalation exposure (Maltoni et al. 1988) or in rats or mice following intermediate or chronic oral exposure (Maltoni et al. 1986; NTP 1988, 1990). Erythema, edema, and increased epidermal thickness were noted in guinea pigs following acute dermal exposure to trichloroethylene (Anderson et al. 1986).

Although human data are not extensive, the data suggest that dermal effects may be a concern for some humans exposed to trichloroethylene, particularly through bathing with contaminated water; however, it is unlikely that exposure to trichloroethylene in the air or soil at hazardous waste sites would be irritating to human skin. Some people may develop immunological sensitivity to trichloroethylene which may manifest as a dermal response following inhalation, oral, or dermal exposure to trichloroethylene.

Ocular Effects. Some humans experienced mild eye irritation following acute inhalation exposure to trichloroethylene at 200 ppm (Stewart et al. 1970). Itchy watery eyes (Baure and Rabens 1974; El Ghawabi et al. 1973) and inflamed eyes (Schattner and Malmck 1990) have been reported following contact with trichloroethylene vapor.

In a chronic oral study in rats, observation of squinting and red discharge from the eyes were reported more frequently in trichloroethylene exposed rats as the study progressed (NCI 1976). Histopathological changes in the eyes were not repotted in rats following chronic inhalation exposure (Maltoni et al. 1988) or in rats or mice following chronic oral exposure (Maltoni et al. 1986; NCI 1976; NTP 1988). Based on the limited data,

it is unknown whether exposure to the trichloroethylene levels found at hazardous waste sites would be harmful to human eyes.

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). In intermediate- and chronic-duration studies body weights less than controls have been reported in animals following inhalation (Adams et al. 1951; Kjellstrand et al. 1983a) and oral exposure (NCI 1976; NTP 1988, 1990) to high levels of trichloroethylene. Body weight effects have not been studied following dermal exposure of animals. Effects on body weight are unlikely to occur in humans exposed to trichloroethylene at levels found in the environment or at hazardous waste sites.

Immunological and Lymphoreticular Effects. It has been suggested that in some cases dermal effects in persons occupationally exposed to trichloroethylene may be sensitivity reactions (Czirjak et al. 1993; Goh and Ng 1988; Phoon et al. 1984). A case study involving excessive skin contact showed that 1 of 11 exposed individuals studied may have had an allergic response to trichloroethylene (Nakayama et al. 1988). People who drank trichloroethylene-contaminated water in Wobum, Massachusetts, had immunological abnormalities, but these people were also exposed to other volatile chlorinated hydrocarbons in the water (Byers et al. 1988; Lagakos et al. 1986b). Symptoms of systemic lupus erythematosus were increased in residents of Tucson, Arizona, exposed to trichloroethylene and other chemicals in drinking water (Kilburn and Warshaw 1992). Diffuse fascitis with eosinophilia was reported in a woman who used well water contaminated with trichloroethylene (Wailer et al. 1994).

There is one animal study indicating that trichloroethylene via the inhalation route alters immune function and resistance to *Streptococcus zooepidemicus* (Aranyi et al. 1986). Another animal study, in which mice were exposed to trichloroethylene in the drinking water, showed treatment-related effects on both cellular- and antibody-mediated immunity; however, the effects did not occur consistently or in a dose-dependent manner (Sanders et al. 1982). Histopathological changes in the spleen have not been reported in animals following intermediate-duration inhalation exposure (Prendegast et al. 1967), or in the spleen or thymus following

acute- (Berman et al. 1995), intermediate-, or chronic-duration (Maltoni et al. 1986; NCI 1976; NTP 1988, 1990) oral exposure to trichloroethylene.

A study in which MRL +/+ mice were treated with trichloroethylene (1,314 mg/kg/treatment) or dichloroacetyl chloride (29.5 mg/kg/treatment) by intraperitoneal injection every 4 days for 6 weeks suggests that these chemicals may accelerate the autoimmune response (Khan et al. 1995). This strain of mice is genetically predisposed to develop systemic lupus erythematosus in the second year of life. Trichloroethylene and dichloroacetyl chloride induced significant increases (45% and 322%, respectively) in serum IgG levels. Significant increases in serum anti-nuclear antibodies, and nonsignificant increases in anti-ssDNA, and anti-cardiolipin were also observed. The study authors suggested that dichloroacetic acid may be the principal metabolite of trichloroethylene responsible for the induction of an autoimmune response, as a dose of trichloroethylene 50-fold greater than the dose of dichloroacetyl chloride was required to induce a response. The limited human data and the limited animal data suggest that in some sensitive people, especially those predisposed to develop autoimmune responses, there may be a concern for immune system effects from exposure to trichloroethylene. However, it is unknown whether exposure to levels of trichloroethylene found in and around hazardous waste sites may result in immune system effects.

Neurological Effects. In the past, trichloroethylene was used as an anesthetic, so it obviously can cause acute central nervous system depression in humans. Also, people have become unconscious after acute exposure to very high levels occasionally present in the workplace (Kohlmuller and Kochen 1994; La&nit and Pietschmann 1960; Longley and Jones 1963; McCarthy and Jones 1983; Steinberg 1981). Human experimental studies revealed mild effects on motor coordination, visual perception, and cognition (Feldman et al. 1985; Rasmussen et al. 1993a, 1993c, 1993d; Vernon and Ferguson 1969). Workers acutely exposed to relatively high levels of trichloroethylene have also complained of adverse effects similar to those seen in the experimental subjects. Nonspecific neurological effects from trichloroethylene exposure in the workplace have been reported and include dizziness and drowsiness, which are similar to the effects of acute inhalation exposure. These effects are generally reversible. An acute-duration inhalation MRL of 2 ppm was derived based on a study in which these subjective neurological effects were noted in exposed humans (Stewart et al. 1970). Evidence from acute and chronic exposures suggest that trichloroethylene causes adverse neurological effects such as dysfunction of cranial nerves (Barret et al. 1987; Buxton and Hayward 1967; Dogui et al.

1991; Feldman et al. 1970, 1985, 1988, 1992; Kilbum and Warshaw 1993; Rasmussen et al. 1993a; Ruijten et al. 1991). Accidental ingestion of trichloroethylene has resulted in delirium and loss of consciousness (Morreale 1976; Perbellini et al. 1991; Stephens 1945; Todd 1954). Studies of persons exposed to trichloroethylene and other chemicals in drinking water do not show conclusive evidence of neurological effects. Neurological complaints were not increased in the Wobum, Massachusetts, population (Byers et al. 1988; Lagakos et al. 1986a). Further examination of a subset of this population did reveal some evidence of cranial nerve damage (Feldman et al. 1988). In the Tucson, Arizona, population exposed to trichlorethylene, decrease in blinking reflex, eye closure, choice reaction time, and intelligence scores (Kilbum and Warshaw 1993), and impaired balance (Kilbum et al. 1994) were noted. Among persons in the ATSDR exposure subregistry, a statistically significant impairment in hearing was reported in children age 9 years or younger (ATSDR 1994; Burg et al. 1995). All of these studies are limited by exposure to multiple chemicals, and a lack of individual exposure data. Direct emersion of the hand (Sato and Nakajima 1978) or thumb (Stewart and Dodd 1964) into trichloroethylene has been reported to be painful.

It is not clear if the effects on cranial nerve dysfunction from inhalation exposure in humans are attributable to trichloroethylene alone or its decomposition products. For example, while a number of limited studies report neuropathies associated with exposure to trichloroethylene (Bardodej and Vyskocill956; Barret et al. 1987; Lawrence and Partyka 1981; McCunney 1988), there are studies which report that these effects resulted from exposure to the trichloroethylene decomposition product, dichloroacetylene (Buxton and Hayward 1967; Cavanagh and Buxton 1989; Feldman 1970; Humphrey and McClelland 1944). Barret et al. (1992) showed that neuropathies in animals resulted from treatment with both trichloroethylene and dichloroacetylene, though the effects from dichloroacetylene were more severe.

Neurological effects in animals exposed to trichloroethylene in the air include hearing loss (Albee et al. 1993; Crofton and Zhao 1993; Jaspers et al. 1993; Rebert et al. 1991), visual impairment (Blain et al. 1992; Kulig 1987; Niklasson et al. 1993), behavioral effects (Adams et al. 1951; Grandjean 1960; Silverman and Williams 1975), and cardiac arrhythmia (Arito et al. 1993, 1994a, 1994b). An intermediate-duration inhalation MRL of 0.1 ppm was derived based on a study in which effects on heart rate and sleep cycles were noted in exposed rats (Arito et al. 1994a). Neurological effects noted in animals following acute oral exposure include increased rearing activity (Moser et al. 1995), transient ataxia (Narotsky et al. 1995) increased performance in a swim test, and decreased brain myelination (Isaacson et al. 1990). Following

chronic-duration oral exposure of rats effects noted included ataxia, lethargy, convulsions, and hind limb paralysis (NTP 1988). In a chronic-duration oral study in mice, excitation followed by a subanaesthetic state was observed in mice shortly after daily gavage treatment with trichloroethylene (Henschler et al. 1984). The available evidence suggests that humans may be at risk for neurological effects from exposure to trichloroethylene at levels found in the environment and near waste sites.

Reproductive Effects. Operating room nurses exposed to trichloroethylene have been reported to have an increased incidence of miscarriages, but they were exposed to many other anesthetics as well (Corbett et al. 1974). Survey results of 1,926 women who had spontaneous abortions revealed a greater risk of abortion associated with trichloroethylene exposure (Windham et al. 1991). This study is limited by multiple chemical exposure. Humans exposed to trichloroethylene in the drinking water in certain areas of the country have not shown adverse reproductive effects (Byers et al. 1988; Freni and Bloomer 1988; Lagakos et al. 1986a).

Inhalation exposure of mice to trichloroethylene has resulted in an increase in abnormal sperm (Beliles et al. 1980; Land et al. 1981). No effects on spermatic micronuclei frequency were observed in mice exposed to trichloroethylene in air for 5 days (Allen et al. 1994). Treatment-related reproductive effects were not observed in female rats exposed to trichloroethylene in air for 2 weeks before mating (Dorfmueller et al. 1979). Mating behavior has been shown to be affected in mice exposed by gavage to high doses of trichloroethylene (Zenick et al. 1984). This effect was considered secondary to the narcotic effects of trichloroethylene. Except for increased testes weight (NTP 1986b) effects on reproductive performance have not been observed in continuous breeding studies of rats (NTP 1986b) or mice (NTP 1985) exposed orally to trichloroethylene. No effects on female fertility were noted in rats treated by gavage with trichloroethylene in corn oil for 2 weeks before mating (Mattson et al. 1984). Histopathological changes in reproductive organs have not been 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). Based on available evidence, exposure to trichloroethylene in air, water, or soil at hazardous wastes sites is not expected to adversely affect human reproduction.

Developmental Effects. There is limited evidence that oral exposure to trichloroethylene, in drinking water, may cause birth defects. However, the existing database contains limited positive as well as limited negative reports. Taken together, these data are inconclusive regarding teratogenic effects in humans exposed to TCE. Over 2,000 male and female workers who were exposed to unspecified concentrations of trichloroethylene and other solvents in the workplace were studied; an increase in malformations was not observed (Tola et al. 1980). An apparent doubling of risk was associated with effects on birth weight among the newborn of women exposed occupationally or nonoccupationally to unspecified concentrations of trichloroethylene (Windham et al. 1991). However, there was no association when general solvent exposure was examined. In both studies complete medical records were not provided. There is some evidence that exposure to trichloroethylene in drinking water may cause certain types of birth defects. However, this body of research is still far from conclusive. A survey of live births and fetal deaths in an area of New Jersey with contaminated public drinking water found an association between trichloroethylene and oral cleft, central nervous system, neural tube defects, and major cardiac defects (Bove et al. 1995). Uncertainty regarding exposure classification and small numbers of cases were the main limitations of this study. In a study of residents exposed to drinking water contaminated with solvents including trichloroethylene, in Wobum, 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). An additional study of the Wobum population has been completed (MDPH 1994). The study authors indicate that there were increased prevalence in choanal atresia, a rare respiratory defect, and hypospadias/congenital chordee among those ever exposed. However, these findings are limited by the small number of cases in which these effects were observed. The study authors cautioned that their study did not rule ;rut moderate increases in rates of the less common adverse reproductive outcomes. For these outcomes only large increases would have been detected. Overall, this study did not show any statistically significant associations between exposure concentration and birth defects. A study of Michigan residents exposed to trichloroethylene and other solvents in their drinking water found no significant excesses of congenital defects or adverse pregnancy outcomes. In this study, sample size was small and the period of exposure was ill-defined (Freni and Bloomer 1988). Another population, in Tucson,

Arizona, was exposed to trichloroethylene in drinking water and had increased numbers of congenital heart defects (Goldberg et al. 1990).

Among persons in the ATSDR exposure subregistry, a statistically significant impairment in hearing was reported in children age 9 years or younger (ATSDR 1994; Burg et al. 1995). Because the time of onset for hearing loss is not available, it is not known if this effect may be a result of *in utero* exposure or exposure after birth. The study authors cautioned that their study does not identify a causal relationship between trichloroethylene and effects but does suggest areas for further research.

Both Bove et al. (1995) and MDPH (1994) examined effects of trichloroethylene exposure on fetal birth weights. Neither study saw a conclusive effect on birth weight, although birth weights tended to be lower in exposed infants compared to controls in the MDPH (1994) study. A small effect on birth weight in male infants was noted in an interim report on adverse birth outcomes for a population living at Camp LeJeune, North Carolina (ATSDR 1997). The women were exposed sometime during gestation. The study authors cautioned that the small group size weakens the causal association and stated that further analyses are ongoing.

Several animal studies using both the inhalation (Beliles et al. 1980; Dorfmueller et al. 1979; Hardin et al. 1981; Schwetz et al. 1975) and oral (Cosby and Dukelow 1992; Manson et al. 1984; NTP 1985, 1986, 1990) routes of exposure did not reveal teratogenic effects on the developing fetus. Decreased litter size and increases in micro- or anophthalmia have been noted in the offspring of rats treated with trichloroethylene during gestation at maternally toxic (deaths, decreased body weight gain) doses (Narotsky and Kavlock 1995; Narotsky et al. 1995). Studies that looked at more sensitive neurological and neurobehavioral effects on developing pups and fetuses (changes in rearing open field activity, exploratory behavior) have found an effect from trichloroethylene exposure (Fredriksson et al. 1993; Isaacson and Taylor 1989; Taylor et al. 1985). The Fredriksson et al. (1993) study was used to derive an acute-duration oral exposure MRL of 0.2 mg/kg/day. A nonmammalian avian embryo model of cardiac teratogenesis was used to examine the question of whether trichloroethylene causes cardiac malformations (Loeber et al. 1988). White Leghorn chick eggs were exposed to 5-25 µM (2-28 µg /g body weight) trichloroethylene injected into the air space of the egg during various stages of incubation. Cardiac malformations, including septal defects, abnormal

cardiac muscle, and atrioventricular canal defects, were found in 7.3% of exposed hearts compared to 2.3% and 1.5% of saline-treated and mineral oil-treated controls. This was a well-conducted study with adequate controls and selection of doses. A study with rats found evidence of abnormal heart development in fetuses from exposed dams (Dawson et al. 1993). A study regarding the teratogenicity of trichloroacetic acid in rats indicates that this metabolite of trichloroethylene can also result in cardiac defects (Smith et al. 1989). In offspring of rats treated by gavage with 0, 330, 800, 1,200 or 1,800 mg/kg/day trichloroacetic acid in water on gestation days 6-15, l%, 5%, 24%, 47%, and 95% of the fetuses, respectively had cardiac defects. Maternal toxicity (decreased body weight gain, increased kidney and spleen weights) was observed at doses of 800 mg/kg/day and greater. Developmental effects may be a concern for some persons exposed to trichloroethylene; however, it is unknown whether exposure to levels of trichloroethylene found in and around hazardous waste sites may result in adverse developmental effects.

Genotoxic Effects. Data regarding the genotoxicity of trichloroetbylene suggest that it is a very weak, indirect mutagen (EPA 1985c). The potential for heritable gene mutations and the mechanisms of carcinogenicity are not known. 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 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

TABLE 2-4. Genotoxicity of Trichloroethylene *In Vivo*

Species (test system)	End point	Results	Reference
Drosophila melanogaster	Chromosomal aberrations	–	Beliles et al. 1980
Mammalian cells:			
Human (occupational exposure)	Chromosomal aberrations	+	Rasmussen et al. 1988
Mouse (spot test)	Gene mutation	(+)	Fahrig 1977
Mouse	Dominant lethal mutation	–	Slacik-Erben et al. 1980
Mouse	Micronucleus formation	+/–	Duprat and Gradiski 1980
Mouse	Micronucleus formation	–	Allen et al. 1994
Mouse	Micronucleus formation	–	Kligerman et al. 1994
Mouse	Chromosomal aberrations	–	Kligerman et al. 1994
Mouse	Sister chromatid exchange	–	Kligerman et al. 1994
Rat	Micronucleus formation	+	Kligerman et al. 1994
Rat	Chromosomal aberrations	–	Kligerman et al. 1994
Rat	Sister chromatid exchange	–	Kligerman et al. 1994
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 (alkaline unwinding assays)	DNA damage (single-strand breaks)	+	Nelson and Bull 1988
Mouse	DNA damage (single-strand breaks)	+	Walles 1986
Mouse (alkaline unwinding assay)	DNA damage (single-strand breaks)	+	Nelson and Bull 1988
Rat	DNA damage (single-strand breaks)	+	McLaren et al. 1994

TABLE 2-4 (*continued*)

Species (test system)	End point	Results	Reference
Rat (hepatocyte unscheduled DNA synthesis)	DNA damage (unspecified)	–	Mirsalis et al. 1989
Mouse (hepatocyte unscheduled DNA synthesis)	DNA damage (unspecified)	–	Mirsalis et al. 1989
Mouse (hepatocyte unscheduled DNA synthesis)	DNA damage (unspecified)	–	Doolittle et al. 1987
Human (occupational exposure)	Sister chromatid exchange	(+)	Gu et al. 1981
Human (smokers, occupational exposure)	Sister chromatid exchange	+	Seiji et al. 1990
Human (nonsmoker, occupational exposure)	Sister chromatid exchange	–	Seiji et al. 1990
Human (smokers and nonsmokers, occupational exposure)	Sister chromatid exchange	–	Nagaya et al. 1989a
Host-mediated assays:			
Schizosaccharomyces pombe (mouse host-mediated assay)	Gene mutation	–	Rossi et al. 1983[b]
Saccharomyces cerevisiae (mouse host-mediated assay)	Gene mutation	+	Bronzetti et al. 1978[b]

[a]Testing effects of chloral after p[r]etreatment with trichloroethylene
[b]Study involves use of metabolic activators.

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

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 per day. In addition, concomitant exposure to other solvents occurred. In a similar investigation of sister chromatid exchange, negative results tiere 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. 1981). Please refer to Table 2-4 for a further summary of the results of inhalation studies. There is no information on potential genotoxic effects in humans from oral exposure.

The results from *in vivo* animal studies are similarly inconclusive with regard to the genotoxicity of trichloroethylene. These studies have concentrated heavily on trichloroethylene's role in DNA damage, primarily in the form of single-strand breaks. High oral doses of trichloroethylene resulted in single-strand breaks in liver cells of $B6C3F_1$ mice and Sprague-Dawley rats (Nelson and Bull 1988). Differences in dose response and metabolite toxicity suggest differences in the mechanisms of single-strand break induction between the two species. 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). While no direct evidence exists for DNA adduct formation by trichloroethylene, covalent binding to DNA and RNA from various organs in rats and mice after intraperitoneal injection has been observed (Mazzullo et al. 1992).

Other investigators found no evidence for DNA damage in $B6C3F_1$ mice, Fischer-344 rats (Mirsalis et al. 1989), or CD-l mice (Doolittle et al. 1987) following oral trichloroethylene exposure or in male Sprague-Dawley rats following intraperitoneal injection (Parchman and Magee 1982). There was, however, evidence for an increased rate of DNA synthesis in $B6C3F_1$ and CD-l mice (Doolittle et al. 1987; Mirsalis et al. 1989), while no such effect was observed in Fischer-344 rats (Mirsalis et al. 1989). This observation indicates that different mechanisms may exist in different rodent species. In addition, the increased rate of

DNA synthesis, a nongenobxic effect, suggests that trichloroethylene may be carcinogenic without necessarily being genotoxic (Doolittle et al. 1987; Klaunig et al. 1991; Mirsalis et al. 1989). An inhalation study found no significant cytogenic or cell cycle progression effects in C57EW6J mice exposed to up to 5,000 ppm trichloroethylene, although evidence for aneuploidy and increased bone marrow micronuclei formation was found in similarly exposed CD rats (Kligerman et al. 1994). The study authors suggest that, although mice exhibit a greater ability than rats to metabolize trichloroethylene, the pathway involving production of the chloral intermediate (known to induce aneuploidy) is predominant in rats, and the observed effect may be due to formation of this metabolite. Results from these and other animal *in vivo* studies can be found in Table 2-4.

The results gathered from *in vitro* studies are no more conclusive than those from *in vivo* studies. A 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). Stuoies 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). A DNA-protein cross-link study produced negative results for chloral-treated liver nuclei from Fischer-344 rats (Keller and Heck 1988). The outcome was positive when D61 .M yeast was tested for mitotic aneuploidy following trichloroethylene treatment both with and without metabolic activation. The same researchers also assessed gene conversion and reverse mutation following treatment of D7 yeast with trichloroethylene (Koch et al. 1988). The results can be viewed in Table 2-5 but are difficult to evaluate because statistical comparisons were not reported. Finally, an interesting study comparing the effects of stabilized versus unstabilized trichloroethylene on the rate of gene mutation was performed on *Salmonella typhimurium.* As seen in Table 2-5, mixed results were found according to the purity of trichloroethylene and the type of assay performed (preincubation or vapor). However, the trichloroethylene stabilizers alone generated positive outcomes for both types of assay (McGregor et al. 1989). The results of other prokaryotic and fungal studies can be found in Table 2-5.

Although trichloroethylene itself may not be genotoxic, several of its metabolites are reactive and potentially genotoxic compounds (Miller and Guengerich 1982). Several isomers of 1,2-dichlorovinyl-cysteine, a product of trichloroethylene metabolism in the kidney, are mutagenic in the *in vitro* Ames assay

TABLE 2-5. Genotoxicity of Trichloroethylene *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Prokaryotic organisms:				
Salmonella typhimurium (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	+	+	McGregor et al. 1989
S. typhimurium (TCE stabilizers, preincubation assay)[a]	Gene mutation	No data	+	McGregor et al. 1989
S. typhimurium (TCE stabilizers, vapor assay)[a]	Gene mutation	No data	+	McGregor et al. 1989
S. typhimurium TA100 (reverse mutation)	Gene mutation	–	–	Waskell 1978
S. typhimurium TA100 (reverse mutation)	Gene mutation	(+)	–	Baden et al. 1979
S. typhimurium TA1535 (reverse mutation)	Gene mutation	+/–	+/–	Baden et al. 1979
S. typhimurium TA1535 (reverse mutation)	Gene mutation	–	–	Shimada et al. 1985
S. typhimurium TA98 (reverse mutation)	Gene mutation	–	–	Waskell 1978
Escherichia coli (forward and reverse mutation)	Gene mutation	+/–	No data	Greim et al. 1975

TABLE 2-5 (*continued*)

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Eukaryotic organisms:				
Fungi:				
Saccharomyces cerevisiae D7 (stationary-phase/production of prototrophic colonies)	Gene conversion	–	–	Koch et al. 1988[b]
S. cerevisiae D7 (log-phase/ production of prototrophic colonies)	Gene conversion	–	–	Koch et al. 1988[b]
S. cerevisiae D7 (stationary-phase/production of prototrophic colonies)	Gene mutation	(+)	(+)	Koch et al. 1988[b]
S. cerevisiae D7 (log-phase/ production of prototrophic colonies)	Gene mutation	(+)	(+)	Koch et al. 1988[b]
S. cerevisiae (reverse mutation)	Gene mutation	No data	–	Callen et al. 1980
S. cerevisiae (reverse mutation)	Gene mutation	+	–	Bronzetti et al. 1980
Schizosaccharomyces pombe (forward mutation)	Gene mutation	–	–	Rossi et al. 1983
Aspergillus nidulans (forward mutation)	Gene mutation	No data	+	Crebelli et al. 1985
S. cerevisiae (gene conversion)	Recombination	No data	+	Callen et al. 1980
S. cerevisiae (gene conversion)	Recombination	+	–	Bronzetti et al. 1978
S. cerevisiae (homozygosis by recombination or gene conversion)	Recombination	No data	+	Callen et al. 1980
A. nidulans (gene cross over)	Recombination	No data	(+)	Crebelli et al. 1985

TABLE 2-5 (*continued*)

Species (test system)	End point	Results		Reference
		With activation	Without activation	
S. cerevisiae D61.M (loss of dominant color homolog)	Mitotic aneuploidy	+	+	Koch et al. 1988
Mammalian cells:				
Rat liver nuclei (chromatographically separated DNA fractions)	DNA-protein cross-links	–	No data	Keller and Heck 1988[c]
Rat primary hepatocytes (unscheduled DNA synthesis)	DNA damage	No data	–	Shimada et al. 1985
C3T3 mouse cells (BALB cell transformation assay)	Cell transformation	No data	(+)	Tu et al. 1985
Rat embryo cells (transformation)	Cell transformation	No data	+	Price et al. 1978
Syrian hamster embryo cells (clonal assay)	Cell transformation	No data	–	Amacher and Zelljadt 1983
Human lymphocytes (unscheduled DNA synthesis)	DNA damage	+/–	+/–	Perocco and Prodi 1981
Human WI-38 (unscheduled DNA synthesis)	DNA damage	(+)	(+)	Beliles et al. 1980

[a]Stabilizers used were oxiranes (1,2-epoxybutane and epichlorohydrin).
[b]Results not statistically compared with others in the study
[c]Testing effects of chloral,, a metabolite of trichloroethylene

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

](Commandeur et al. 1991; Dekant et al. 1986c). These products have been identified in the urine of workers exposed to trichloroethylene (Bimer et al. 1993). Although trichloroethylene itself may not be genotoxic, the evidence that some of its metabolites are genotoxic suggests that genotoxic effects may be a concern for some persons exposed to trichloroethylene. However, it is unknown whether exposure to levels of trichloroethylene found in and around hazardous waste sites may result in genotoxic effects.

Cancer. Workers who have been exposed to trichloroethylene show no higher incidence of cancer than controls in numerous epidemiologic studies (Axelson et al. 1978; Hardell et al. 1981; Malek et al. 1979; Novotna et al. 1979; Paddle 1983; Spirtas et al. 1991; Tola et al. 1980). Studies that did show an increased incidence of specific cancers in exposed workers were complicated by exposures to other chemicals, including known human carcinogens (Antilla et al. 1995; Blair et al. 1979; Hardell et al. 1994; Henschler et al. 1995). A population that drank contaminated well water in Wobum, Massachusetts, was reported to have an increase in childhood leukemia (Lagakos et al. 1986a). This was supported by a second study of New Jersey communities, which were served by a community water system, where an increase in the standardized mortality ratio for leukemia was found in females exposed to trichloroethylene (Pagliano et al. 1990). Further expansion of the New Jersey population showed a significant elevation of total leukemias, childhood leukemias, acute lymphatic leukemias, and non-Hodgkin's lymphoma in females exposed to >5.0 ppb trichloroethylene (Cohn et al. 1994). Diffuse large celVreticulosarcoma non-Hodgkin's lymphoma was significantly elevated in males as well. A retationship between trichloroethylene exposure in drinking water and cancer including non-Hodgkin's lymphoma, multiple myeloma, and leukemia was not observed in a Finnish study (Vartianinen et al. 1993). Problems associated with these studies, including exposure to a mixture of chemical contaminants and, particularly in the Lagakos et al. (1986a) study, the use of statistical methods which have been questioned by others (MacMahon 1986; Prentice 1986; Rogan 1986; Swan and Robins 1986; Whittemore 1986). Thus, the associations drawn from these studies between the incidence of leukemia and other cancers and the oral exposure to trichloroethylene are suggestive yet inconclusive. Data in the ATSDR trichloroethylene subregistry indicate an excess number of deaths from respiratory cancer in men exposed environmentally to trichloroethylene when compared with national survey data (ATSDR 1994). The study authors concluded that based on the incidence of smoking in the population "it would be inappropriate to relate this excess solely to trichloroethylene exposure."

Animal studies have shown increases in various types of cancer following inhalation or oral exposure to trichloroethylene, including cancer of the liver in mice (NCI 1976; NTP 1990) and cancer of the kidney (NTP 1988, 1990) and testes (NTP 1988) in rats. A serious problem with many of the studies is poor survival rate (Maltoni et al. 1986; NTP 1988,1990). Also, some of the studies used trichloroethylene containing small amounts of epoxide stabilizers to preserve the trichloroethylene from rapid degradation. Since these epoxides form free radicals, they themselves may be carcinogens and may contribute to the carcinogenic potential of industrial trichloroethylene. An NTP study using epoxide-free trichloroethylene showed liver tumors in mice, some indication of renal tumors in male rats, and no evidence of carcinogenicity in female rats (NTP 1990). Acute oral exposure to trichloroethylene or its metabolites preferentially induces peroxisome proliferation in mouse liver, which may be related to the carcinogenic response in this species (Goldsworthy and Popp 1987).

In addition, it has been hypothesized that some of the potential for tumor induction may be related to formation of trichloroethylene metabolites such as DCA, TCA, chloral hydrate, and 2-chloroacetaldehyde (Daniel et al. 1992; DeAngelo et al. 1991; Larson and Bull 1992a). The greater trichloroethylene-induced carcinogenicity in mice compared to the rat is believed by some investigators to be related to the increased conversion of the parent compound by mice to the reactive metabolites and the saturation of metabolism at higher dose levels in rats (Dallas et al. 1991; Dekant et al. 1986b; Filser and Bolt 1979; Larson and Bull 1992a; Prout et al. 1985; Stott et al. 1982). Direct administration of DCA and TCA in the drinking water resulted in an increased incidence of liver tumors in the mouse, while administration of trichloroethylene did not (Herren-Freund et al. 1987).

Trichloroethylene has been nominated for listing in the National Toxicology Program's (NTP) 9th Report on Carcinogens. Evaluation of this substance by the NTP review committees is ongoing. Based on limited evidence in humans, and sufficient evidence in animals for carcinogen&city, IARC (1995) considers trichloroethylene probably carcinogenic to humans (2A). ACGIH has placed trichloroethylene in their group A5, not suspected as a human carcinogen (ACGIH 1996). This group is for chemicals not suspected to be human carcinogens on the basis of properly conducted epidemiologic studies in humans. The studies reviewed were considered to "have sufficiently long follow-up, reliable exposure histories, sufficiently high dose, and adequate statistical power to conclude that exposure to the agent does not convey a significant risk of cancer to humans."

The incidence data for lung tumors in female Swiss mice together with tumor incidence data from other studies were used by EPA (1987a) to derive a carcinogenic potency estimate; a classification of B2 (probable human carcinogen) was assigned to trichloroethylene. In 1988, the Scientific Advisory Board for the EPA offered an opinion that the weight-of-evidence was on a C-B2 continuum (possible-probable human carcinogen). The agency has not restated a more current position on the weight-of-evidence classification and is reflecting this by posting an "under review" status in IRIS (IRIS 1996).

It has been argued that occupational studies do not suggest that trichloroethylene is a potent carcinogen, given the enormous size of the workforce exposed to the chemical and the small number of persons experiencing carcinogenic effects (Abelson 1993; Kimbrough et al. 1985; Steinberg and DeSesso 1993). Kimbrough et al. (1985) further maintain that, although trichloroethylene has been shown to be a weak-to-moderate carcinogen in mice and rats, there are differences between low- and high-dose metabolism in animals and differences between species in susceptibility to cancer. They suggest the possibility that metabolism to a proximate carcinogen does not occur in humans at low doses. In general, the associations drawn from the limited epidemiological data in humans, as well as cancer studies in animals, are suggestive yet inconclusive. Based on the available data, cancer should be an effect of concern for people exposed to trichloroethylene in the environment and at hazardous waste sites.

2.6 BIOMARKERS OF EXPOSURE AND EFFECT

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

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound 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 2.6.1.

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 2.6.2.

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 2.8, Populations That Are Unusually Susceptible.

2.6.1 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-l 1%) of the absorbed dose is exhaled as unchanged trichloroethylene

through the lungs, and 2% of the dose is eliminated by the lungs as trichloroethanol. A correlation was 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.

There are three biological exposure indices (BEIs) for exposure to trichloroethylene at the ACGIH threshold limit value time-weighted average (TLV-TWA) of 50 ppm (ACGIH 1996). When measured at the end of a 40-hour workweek, TCA in urine is approximately 100 mg/g creatinine; when measured at the end of an 8-hour shift at the end of a workweek TCA and trichloroethanol in urine is approximately 300 mg/g creatinine, and free trichloroethanol in blood is approximately 4 mg/L.

Monitoring for exposure to trichloroethylene has also been performed by measuring trichloroethylene and its principal metabolites (TCA, trichloroethanol, trichloroethanol glucuronide) in blood and urine (Ertle et al. 1972; Ikeda et al. 1972; Imamura and Ikeda 1973; Kimmerle and Eben 1973b; Monster et al. 1979; Mtiller 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).

The use of the methods for monitoring metabolites of trichloroethylene in blood and urine is, however, 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 men secrete more trichloroethanol than women (Inoue et al. 1989). The use of the level of trichloroethylene adduction to blood proteins as a quantitative measure of exposure is also possible, although obtaining accurate results may be complicated by the fact that several metabolites of trichloroethylene may also form adducts (Stevens et al. 1992).

Differences 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 tricbloroethylene will tend to decrease the amount exhaled after a workshift. Increased renal function 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.

Urinary concentration of the renal tubular enzyme N-acetyl-β-D-glucosaminidase (NAG) has been used as an indicator of renal damage resulting from trichloroethylene exposure, although part of this effect may have been age dependent (Brogren et al. 1986). Other studies specifically examining the influence of factors such as age or alcohol consumption on the association 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 dosedependent 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 recommending this assay as a sensitive indicator of low-level exposure (Bai and Stacey 1993; Hamdan and Stacey 1993). However, 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).

Ambient air monitoring remains the best predictor of external exposure to trichloroethylene. Based on results using a mathematical model, measurements of TCA levels are considered the best indicator oflong-term exposure to trichloroethylene; the level of TCA in urine before workshift exposure is regarded as a predictor of the average exposure over days (Femandez et al. 1977). Accordingly, the measurement of urine levels of trichloroethanol may give a better indication of recent exposure.

2.6.2 Biomarkers Used to Characterize Effects Caused by Trichloroethylene

The system that is most sensitive to acute toxicity from inhalation exposure to trichloroethylene is the nervous system. 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 decomposition product. Conclusive studies distinguishing the toxicity of trichloroethylene, its decomposition products, 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 trichloroetbylene exposure in the water (Feldman et al. 1988). Although this test has only been used in the past to differentiate group differences (because of the lack of individual exposure data), it is possible that further refinements of this technique may make it useful as a biomarker in the future. 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 (Amler et al. 1995; Arezzo et al. 1985; Baker et al. 1985; WHO 1990).

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 β_2-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 β_2-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 (β_2-microglobulin and N-acetyl-β-D-glucosaminidase) are used to indicate 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 protein levels have been used to assess exposure to trichloroethylene (Capellini and Grisler 1958; Konietzko and Reill 1980; Rasmussen et al. 1993b).

2.7 INTERACTIONS WITH OTHER SUBSTANCES

Alcohol can affect the metabolism of trichloroethylene. This is noted in both toxicity and pharmacokinetic studies. In toxicity studies, simultaneous exposure to ethanol and trichloroethylene increased the concentration of trichloroetitylene in the blood and breath of male volunteers (Stewart et al. 1974~). These people also showed “degreaser’s flush”-a transient vasodilation of superficial skin vessels. In rats, depressant effects in the central nervous system are exacerbated by coadministration of ethanol and trichloroethylene (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 a long time interval after ethanol administration, and subsequent enzyme induction, trichloroethylene metabolic rates would be expected to increase. This may be the explanation for 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, reflecting a more reduced state in the hepatocyte (Larson and Bull 1989).

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, these compounds increased the steady-state concentration of trichloroethylene in the venous blood (Jakobson et al. 1986). Treatment with disulfiiam 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 4064% and 72-87%, respectively. Pretreatment with phenobarbital and 3-methylcholanthrene, which, like ethanol, are inducers of the liver mixed-function oxidase system, increased the extent of liver injury following exposure to trichloroethylene (Carlson 1974). Similar results were found with other inducers of the hepatic mixed-function oxidase system (Allemand et al. 1978; Moslen et al. 1977; Nakajima et al. 1990b). By enhancing the metabolism of trichloroethylene to its cytotoxic metabolites, compounds that induce the hepatic mixed-function oxidase system can potentiate the hepatotoxicity of trichloroethylene.

Animal studies indicate that trichloroethylene can sensitize the heart to epinephrine-induced arrhythmias. 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 also been found to increase the incidence of epinephrine-induced arrhythmias in rabbits exposed to trichloroethylene (White and Carlson 1982).

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, 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 alanine aminotransferase 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 enzyme 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.

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. 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 pahnitoyl CoA oxidation activity (Goldsworthy and Popp 1987). Rats injected with mixtures of benzene and trichloroethylene generally showed inhibited benzene metabolism as measured by conjugated phenol excretion (Starek 1991). At higher doses of trichloroethylene (5 mmol/kg), conjugated phenol excretion was lower directly after exposure, but higher than in the rat exposed to benzene alone 2 days after exposure. Additional reports include potentiation of the hepatotoxicity of carbon tetrachloride by trichloroethylene in rats (Pessayre et al. 1982) and competitive inhibition of P-450 metabolism by mixtures of vinyl chloride and trichloroethylene in rats, as determined by PBPK modeling and *in vitro* studies (Barton et al. 1995).

In degreasing operations, there may be exposures to carbon monoxide, which may compound symptoms reported by workers (NIOSH 1973). Illnesses of certain employees, documented at a neighboring hospital, included headache, nausea, dizziness, and chest pain. The NIOSH report concluded that the first employee illness reports were due to toxic effects of carbon monoxide complicated by trichloroethylene exposure. The

source of carbon monoxide was propane for lifts, and the trichloroethylene source was a malfunctioning degreaser.

2.8 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 5.6, 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. If the metabolic products are more toxic than the parent compound, an individual with higher metabolic rates (such as some children and adolescents) would be expected to have greater 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. People who smoke may increase their risk of toxic effects from trichloroethylene. However, these data are equivocal and limited. People who consume alcohol or who are treated with disulf'ii may be at greater risk of trichloroethylene poisoning because ethanol and disulfii 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 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.

The metabolism of trichloroethylene, as measured by the levels of excreted urinary metabolites, differs significantly between men and women, although study results are inconsistent (Inoue et al. 1989; Kimmerle and Eben 1973b; Norniyama and Nomiyama 1971). It does appear, however, that women excrete more urinary TCA than do men (Kimmerle and Eben 1973b; Nomiyama and Nomiyama 1971). Testosterone has been implicated as a factor in the lower absorption of trichloroethylene in male rats compared with females (Kadry et al. 1991b; McCormick and Abdel-Rahman 1991), and the same effect may occur in humans.

2.9 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to trichloroethylene. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to trichloroethylene. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to trichloroethylene: Bronstein and Currance 1988; Ellenhom and Barceloux 1988; Stutz and Janusz 1988.

2.9.1 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. Externally, trichloroethylene can produce mild irritation; chronic exposure may produce a rash and chapped skin (HSDB 1994). Exposed skin should be washed thoroughly with soap and water. Exposed eyes should be flushed with a clean neutral solution such as water or normal saline for 15-20 minutes (HSDB 1994). One source recommends inducing emesis within 30 minutes of a substantial ingestion unless the patient is or could rapidly become intoxicated, comatose, or convulsive (HSDB 1994). Absorption of trichloroethylene in water was found to be more than three times greater than absorption after administration in corn oil (Withey et al. 1983). Use of an activated charcoal slurry, aqueous or mixed with saline cathartic or sorbitol, has also been advocated as a mitigation strategy to diminish absorption in persons who have ingested trichloroethylene (HSDB 1994). Researchers have found that the presence of food in the stomach decreases oral absorption of the chemical and that

gastrointestinal absorption from an aqueous vehicle occurs at a very rapid rate (D'Souza et al. 1985). Thus, any attempt to reduce absorption must be instituted very soon after ingestion has occurred.

2.9.2 Reducing Body Burden

Trichloroethylene is exhaled following inhalation and oral exposures (Dallas et al. 1991; Koizumi et al. 1986; Stewart et al. 1970), whereas metabolites are mainly excreted in the urine (Femandez et al. 1977; Koizumi et al. 1986; Monster et al. 1979; Sato et al. 1977). Based on the knowledge of trichloroethylene metabolism and excretion, potential methods for reducing the body burden are presented. These methods have not been used in persons or animals exposed to trichloroethylene and should be researched further before being applied.

Mitigation strategies to increase urinary output and dilute the trichloroethylene once it is in the bloodstream seem useful. One method for this may be increased hydration of the individual in order to stimulate diuresis. Although flushing the gastrointestinal system by gastric lavage is sometimes suggested, it is contraindicated in the case of trichloroethylene poisoning because it is cumbersome in cases of ingestion of a rapidly absorbed liquid like trichloroethylene and may result in serious compromise to the electrolyte balance of the individual.

Studies suggest that a large percentage of trichloroethylene absorbed upon inhalation or oral exposure is metabolized in the liver via the cytochrome P-450 system (Buben and CWlaherty 1985; Ertle et al. 1972; Femandez et al. 1977; Green and Prout 1985; Kimmerle and Eben 1973a, 1973b; Monster et al. 1976,1979; Mtiller et al. 1972; Prout et al. 1985; Sato et al. 1977; Soucek and Vlachova 1960; Stott et al. 1982; Vesterberg and Astrand 1976). The major metabolites for trichloroethylene are trichloroethanol, TCA, and trichloroethanol-glucuronide conjugate. Although GSH plays a relatively minor role in metabolism of moderate doses of trichloroethylene, GSH may be more important in reacting with trichloroethylene oxide in high-dose situations. Thus, it may aid in reducing cell injury by this reactive epoxide. Administration of drugs which lower GSH levels, such as acetaminophen, may therefore be inadvisable after trichloroethylene exposure. Other sulfhydryl containing compounds, such as cysteine or cysteamine, could also be given instead of GSH.

Attempts to diminish the overall metabolism of trichloroethylene might be useful (e.g., hypothermia, mixed-function oxidase inhibitors, competitive inhibitors of trichloroethylene metabolism [i.e., P-450 substrates]), if instituted soon enough after trichloroethylene exposure. Catecholamines (especially beta agonists) act in concert with trichloroethylene, increasing the risk of cardiac arrhythmias. Hence, catecholamines should be administered to patients only in the lowest efficacious doses and for certain limited presentations of trichloroethylene poisoning. 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.

Information on the distribution of trichloroethylene is limited and provides little insight on how distribution might be altered to facilitate any attempts at mitigation of effects. One study reported distribution of ^{14}C-trichloroethylene to the liver, skin, and kidney following drinking water exposure (Koizumi et al. 1986). These data were comparable to those reported by Stott et al. (1982) following inhalation exposure. Evidence for the redistribution of trichloroethylene to fat over time and some reports of significant accumulation (Savolainen et al. 1977) do not agree with other reports of negligible accumulation (Koizumi et al. 1986).

2.9.3 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 1354; Morreale 1976; Smith 1966). Propanolol is an example of an anti-adrenergic agent that may be useful after exposure to trichloroethylene. This agent acts by blocking β-adrenergic receptors, thus preventing catecholamines such as epinephrine from binding, and 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. Because physical activity appears to increase the chance of cardiac effects, reducing physical exertion after exposure to trichloroethylene may be useful.

2.10 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 health effects (and techniques for developing methods to determine such health effects) of trichloroethylene.

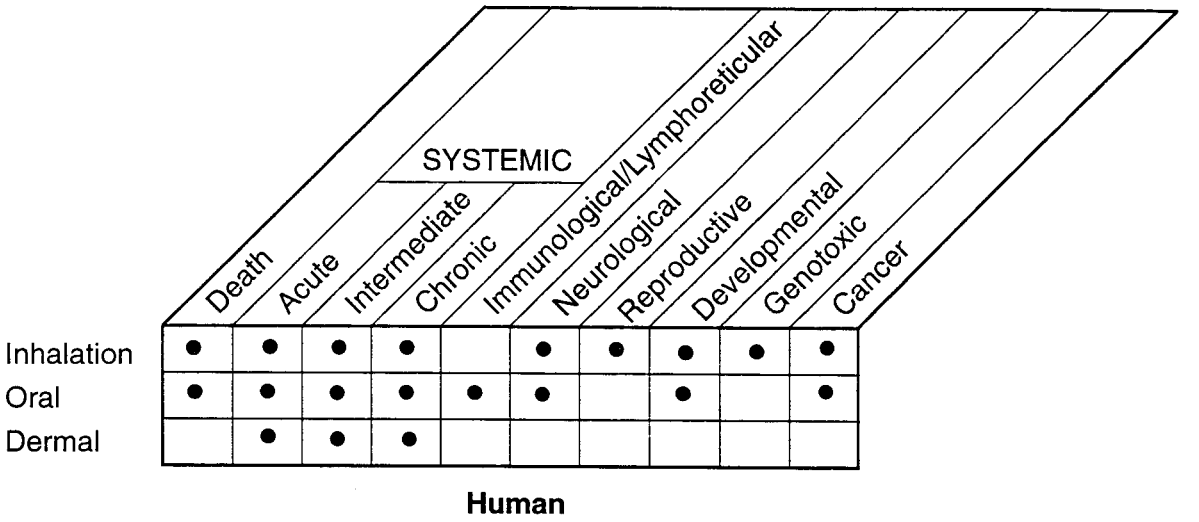
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean 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.

2.10.1 Existing Information on Health Effects of Trichloroethylene

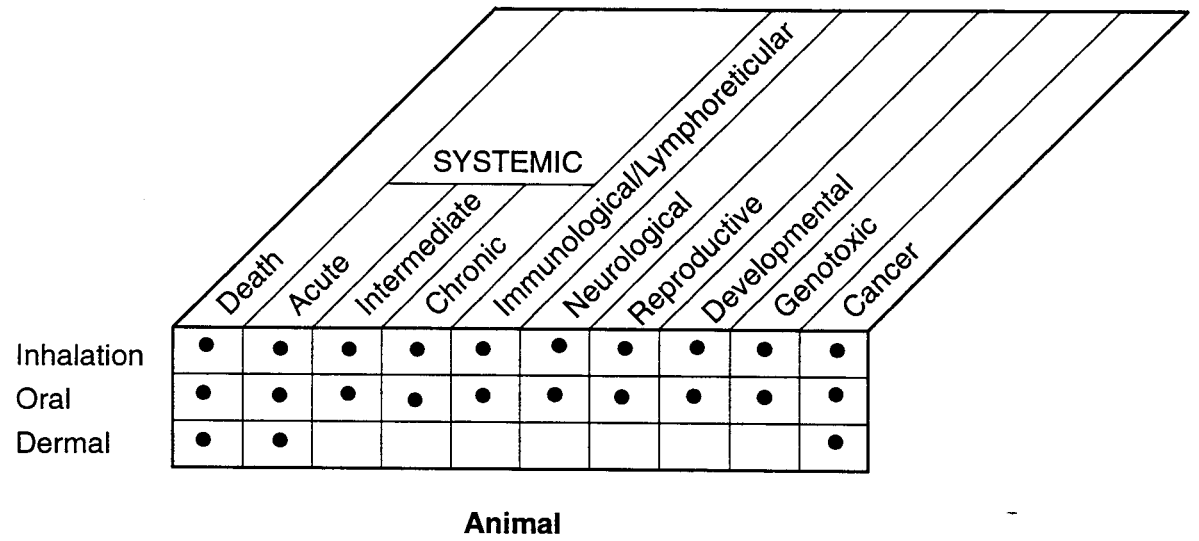
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to trichloroethylene are summarized in Figure 2-5. The purpose of this figure is to illustrate the existing information concerning the health effects of trichloroethylene. Each dot in the figure indicates that one or 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 Identifiing 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 in experiments have provided most of the data on health effects of inhaled tichloroethylene in humans. Most of the information on reported effects in humans following oral exposure

FIGURE 2-5. Existing Information on Health Effects of Trichloroethylene



Human



Animal

● Existing Studies

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 or unquantified. 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, but exposure/dose data are not available.

Studies have been performed in animals that cover all of the health effects areas listed in Figure 2-5 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 but do not fully characterize exposure/dose-effect relationships. Threshold doses are lacking for many of the toxic effects. Some of the effects (e.g., immunosuppression, hematologic effects) need additional characterization, and there is a paucity of data for effects resulting from acute and chronic exposures. One of the significant limitations to interpreting results from most 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 intermittent or continuous exposure to trichloroethylene in air or drinking water.

2.10.2 Identification of Data Needs

Acute-Duration Exposure. 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; Sidorin et al. 1992). 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 excretion. Acute inhalation studies in animals suggest that trichloroethylene sensitizes the heart to catecholamines (Reinhardt et al. 1973; White and Carlson 1979, 1981,1982). Sufficient human and animal information is available to identify the nervous system as the most 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. An acute-duration MRL of 2 ppm for inhalation exposure has been derived on the basis of subjective neurological effects (headache, fatigue, drowsiness) in humans exposed to 200 ppm

trichloroethylene for 5 days, 7 hours/day (Stewart et al. 1970). 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 (Cleat-field 1970; David et al. 1989; DeFalque 1961; Gutch et al. 1965; Lachnit and Pietschmann 1960), mild evidence of liver damage (Cleat-field 1970), and renal failure (David et al. 1989; Gutch et al. 1965). Additional adverse effects noted in animals following acute inhalation exposure to trichloroethylene include hrer damage (Carlson 1974; Fujita et al. 1984; Okino et al. 1991), kidney damage (Crofton and Zhao 1993), and respiratory effects in mice (Odum et al. 1992; Villas&i et al. 1991).

Acute oral LD_{50}s are available from animal studies (Smyth et al. 1969; Tucker et al. 1982). Following acute oral exposure to trichloroethylene effects noted in humans include cardiac effects (Dhuner et al. 1957; Morreale 1976; Perbellini et al. 1991) and neurological effects (Dhuner et al. 1957; Morreale 1976; Perbellini et al. 1991; Stephens 1945; Todd 1954). Effects noted in animals following acute oral exposure to trichloroethylene include hepatic (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 (Berman et al. 1995), and neurological effects (Coberly et al. 1992; Moser et al. 1995; Narotsky and Kavlock 1995; Narotsky et al. 1995). An acute-duration MRL of 0.2 mg/kg/day for oral exposure has been derived on the basis of developmental neurological effects in mice (Fredriksson et al. 1993). The weight of evidence supports nervous system development as a target of trichloroethylene (Isaacson and Taylor 1989; Nolaird-Gerbec et al. 1986; NTP 1986; Taylor et al. 1985), and thus justifies its use in deriving an MRL. However, further studies on the developmental neurological effects of trichloroethylene in both animals and humans are needed to more fully characterize these effects.

Pain and erythema have been reported by study subjects who stuck 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 is needed regarding doses/concentrations that result in cardiac effects and conditions that may make persons more sensitive to these effects.

Further information gained from accidental human exposures could be utilized in defining the lowest air level that affects humans. 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 available on neurological effects after acute inhalation exposure.

Intermediate-Duration Exposure. Intermediate-duration studies of tetrachloroethylene exposure of humans are limited to case reports of people who were occupationally exposed (Mitchell and Parsons-Smith 1969; Phoon et al. 1984; Priest and Horn 1965; Steinberg 1981; Wemisch et al. 1991). Neurological effects were the most consistent effects reported (Mitchell and Parsons-Smith 1969; Steinberg 1981; Wemisch et al. 1991). Trichloroethylene has been studied in animals following intermediate-duration inhalation exposure (Adams et al. 1951; Albee et al. 1993; Arito et al. 1994a; Baker 1958; Battig and Grandjean 1963; Blain et al. 1992,1994; Goldberg et al. 1964a; Haglid et al. 1981; Jaspers et al. 1993; Kimmerle and Eben 1973a; Kjellstrand et al. 1981, 1983a; Kulig 1987; Laib et al. 1979; Okamoto and Shiwaku 1994; Prendergast et al. 1967; Rebert et al. 1991; Silverman and Williams 1975). Effects noted in these studies included neurological effects (Adams et al. 1951; Arito et al. 1994a; Baker 1958; Battig and Grandjean 1963; Blain et al. 1992; Goldberg et al. 1964a; Haglid et al. 1981; Jaspers et al. 1993; Kulig 1987; Rebert et al. 1991; Silverman and Willams 1975), and hepatic effects (Adams et al. 1951; Kjellstrand et al. 1983a). An intermediate-duration inhalation MRL of 0.1 ppm has been derived based on neurological effects in rats (Arito et al. 1994a).

With the exception of studies examining reproductive outcome in people exposed to trichloroethylene in drinking water (ATSDR 1997; MDPH 1994), intermediate-duration studies in humans follow&g oral exposure were not available. Intermediate-duration oral studies of trichloroethylene in animals (Barret et al. 1991,1992; Buben and O'Flaherty 1985; Constan et al. 1995; Dawson et al. 1993; Goel et al. 1992; Isaacson et al. 1990; Mason et al. 1984; Merrick et al. 1989; NCI 1976; NTP 1988,1990; Stott et al. 1982; Tucker et al. 1982; Zenick et al. 1984) are available, but did not adequately provide exposure levels that could be

related to effects. Therefore, an intermediate-duration oral MRL has not been derived. Intermediate-duration dermal studies of trichloroethylene in humans or animals were not available.

Additional animal studies of trichloroethylene following intermediate-duration oral exposure are necessary to further define dose-response relationships. Because developmental neurotoxicity appears to be a sensitive end point, a focus on this end point would be useful. Animals studies following intermediate-duration dermal exposure are necessary. These studies would indicate whether targets following dermal exposure differ compared to inhalation and oral exposure.

Chronic-Duration Exposure and Cancer. Information on humans is available from studies of people exposed to trichloroethylene in the air for chronic periods in the workplace (Barododej and Vyskocil1956; Barret et al. 1987; Bauer and Rabens 1974; El Ghawabi et al. 1973; Kohhrmller and Kochen 1994; Rasmussen et al. 1993c; Ruitjen et al. 1991). These studies indicate that the nervous system may be the most sensitive target. other studies of workers occupationally exposed to trichloroethylene for chronic periods indicate that liver (Bauer and Rabens 1974; Capelliei and Grisler 1958; Schuttman 1970) and kidneys (Brogren et al. 1986) are targets of trichloroethylene. The liver effects noted included increases serum levels of liver enzymes (Bauer and Rabens 1974; Schuttman 1970), and liver enlargement (Capellini and Grisler 1958; Schuttman 1970). The kidney effects noted include increased N-acetyl-β-D-glucosaminidase (Brogren et al. 1986). Information on chronic human exposure to trichloroethylene via the oral route is largely from studies of people who consumed trichloroethylene and other solvents in their drinking water for several years (ATSDR 1994; Bove et al. 1995; Burg et al. 1995; Byers et al. 1988; Cohn et al. 1994; Fagliano et al. 1990; Feldman et al. 1988; Freni and Bloomer 1988; Goldberg et al. 1990; Kilbum 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; Kilbum and Warshaw 1992; Waller et al. 1994), neurological effects (Feldman et al. 1988), an increase in 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 has been established by ATSDR to monitor people living in areas wherethey were exposed to trichloroethylene in drinking water (ATSDR 1994; Burg et al. 1995). The data in the subregistry indicate excess numbers of heart disease and respiratory cancer deaths, as well as stroke, anemia, liver and kidney disease, and hearing and speech impairment. The greatest limitation to these studies is the difficulty in estimating dose, and exposure to multiple chemicals. Some workers who have had dermal contact with

tichloroethylene 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 inhalation MRL was not derived because of the lack of adequate measurement of exposure levels in some studies and/or the lack of effects that could be specifically related to the exposures. Chronic oral exposure studies in animals have focused on carcinogenicity and are not helpful in defining noncancer end points in humans following long-term exposure. Data were not sufficient for the development of a chronic-duration oral MRL. Further epidemiological studies in humans are necessary to help in assessing the risks to persons who live near hazardous waste sites. Additional chronic-duration oral and inhalation studies of trichloroethylene in animals are necessary to further define the thresholds of toxicity. A chronic-duration dermal study in animals may also be useful to identify targets following dermal exposure to trichloroethylene.

Humans exposed to trichloroethylene for chronic periods via the inhalation and dermal routes in the workplace apparently did not experience an increased incidence of cancer, as indicated by numerous epidemiological studies (Axelson 1986; Axelson et al. 1978, 1994; Malek et al. 1979; Shindell and Uhich 1985; Spirtas et al. 1991). I'hese studies are all limited, however, and may not be useful for detecting a weak carcinogen or carcinogens with a long latency period. A number of studies have also shown small but statistically significant associations betweencancer and occupational exposure to trichloroethylene (Antilla et al. 1995; Hat-dell et al. 1994; Henschler et al. 1995). The link between oral exposure to trichloroethylene and cancer in humans is controversial. A number of studies support an association (Byers et al. 1988; Fagliano et al. 1990; Kotelchuck and Parker 1979; Lagakos et al. 1986a; Parker and Rosen 1981), while a number of studies do not provide support for an association between cancer and exposure to trichloroethylene in drinking water (ATSDR 1994; Freni and Bloomer 1988; Vartiainen et al. 1993). These studies are all limited by multiple exposure and the lack of information regarding individual exposure information.

Animal studies have shown that tumors can result from both inhalation (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. Unfortunately, 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 and do not point to a particular target organ for increased tumor incidence. 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 but not female rats. Further studies are necessary to elucidate the mechanisms responsible for the sex and species differences in cancer incidence and to determine whether the processes that operate in the induction of mouse liver cancer by trichloroethylene also operate in the human liver.

Genotoxicity. The genotoxicity studies of trichloroethylene have produced mixed results. Human and *in vivo* animal data exist that suggest that trichloroethylene has genotoxic effects-specifically, sister chromatid exchange, chromosomal aberrations, single-strand breaks, and gene mutations (Gu et al. 1981; Nelson and Bull 1988; Rasmussen et al. 1988; Seiji et al. 1990; Walles 1986). In addition, *in vitro* studies show positive results for gene mutations, recombination, mitotic aneuploidy, and cell transformation (Bronzetti et al. 1978; Callen et al. 1980; Crebelli et al. 1985; Koch et al. 1988; McGregor et al. 1989; Tu et al. 1985). However, many additional studies testing these and other genotoxic effects have been negative (Amacher and Zelljadt 1983; Beliles et al. 1980; Nagaya et al. 1989a; Rossi et al. 1983; Shimada et al. 1985; Slacik-Erben et al. 1980). 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 an increased 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. 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 showed an approximate 3-fold increase in spontaneous abortion in women exposed to trichloroethylene and other solvents (Windham et al. 1991). Significant effects on sperm parameters were not observed in men occupationally exposed to trichloroethylene (Rasmussen et al. 1988). Adverse reproductive effects were not noted in humans that ingested water contaminated with trichloroethylene and other solvents (Byers et al. 1988; Freni and Bloomer 1988; Lagakos et al. 1986a). Available inhalation studies in animals do not fully characterize the reproductive effects following inhalation exposure. Only abnormal sperm morphology has been reported after inhalation exposure; however reproductive performance was not evaluated in these studies

(Beliles et al. 1980; Land et al. 1981). Studies for oral exposure indicate no adverse reproductive effects (NTP 1985, 1986). More research on the reproductive effects of inhalation exposure to trichloroethylene, especially effects on miscarriage in humans is needed. Additional animal studies via the inhalation and dermal routes are needed to further characterize reproductive effects.

Developmental Toxicity. Studies of female workers exposed to trichloroethylene found no correlation between fetal malformation and exposure (Tola et al. 1980) or birth weight and exposure (Windham et al. 1991). An increase in birth defects was observed in nurse-anesthetists who were exposed to trichloroethylene and other anesthetic gases during pregnancy (Corbett et al. 1974). Oral studies have suggested that exposure to trichloroethylene, along with other volatile hydrocarbons, may increase the risk of childhood leukemia (Lagakos et al. 1986b). Another study reported a possible increase in the risk of congenital heart defects (Goldberg et al. 1990) in children whose parents were exposed to trichloroethylene in the drinking water. Adverse developmental outcomes reported in more recent studies include decreased birth weights (Bove et al. 1995; MDPH 1994; ATSDR 1997); choanal atresia, and hypospadias/congenital chordee (MDPH 1994). An increase in hearing impairment in children aged 9 years or younger was reported among participants in the ATSDR exposure subregistry for tricholorehtylene. Though many studies have reported weak associations betweeen oral exposurse to trichloroethylene with other solvents and adverse birth outcomes, at least one report has found no increases in congenital defects from such exposures (Freni and Bloomer 1988). Limitations in the available reports include small numbers of cases, poorly characterized exposures, exposure to multiple solvents, and possible interviewer bias. 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 exisitng database. There are no known studies in humans of developmental effects from dermal exposure to trichloroethylene.

Animal studies regarding developmental effects have been completed using both inhalation (Beliles et al. 1980; Dorfmueller et al. 1979; Hardin et al. 1981; Healy et al. 1982; Schwetz et al. 1975) and oral exposure (Coberly et al. 1992; Cosby and Dukelow 1992; Dawson et al. 1993; Isaacson and Taylor 1989; Manson et al. 1984; Narotsky and Kavlock 1995; Narotsky et al. 1995; Noland-Gerbec et al. 1986; NTP1985, 1986). Following inhalation exposure, the effects noted at concentrations that were not overtly maternally toxic were decreased fetal weight and incomplete ossification (Dorfmueller et al. 1979; Healy et al. 1982). Following oral exposure at maternally toxic doses the effects observed included a significant decrease in litter size and micro- or anophthalmia (Narotsky and Kavlock 1995; Narotsky et al. 1995), increased perinatal mortality (Manson et al. 1984; NTP 1985), an increase in fetal heart abnormalities (Dawson et al. 1993), a decrease in

the number of myelinated fibers in the hippocampus (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). Trichloroacetic acid given to rats by gavage during gestation was also shown to increase heart defects (Smith et al. 1989). An acute-duration oral MRL of 0.2 mg/kg/day was derived based on behavioral changes observed in mice exposed from 10 to 16 days of age (Fredriksson et al. 1993).

Further monitoring for birth defects in humans exposed to trichloroethylene are needed, especially in populations in which exposure concentrations could be determined. Additional studies in animals that develop dose-response relationships for particular defects and trichloroethylene exposure, as well as exposure to metabolites of trichloroethylene, are needed.

Immunotoxicity. Immunological abnormalities were noted in adults who were exposed to contaminated well water and who were family members of children with leukemia (Byers et al. 1988). This was manifested by altered ratios of T-lymphocyte subpopulations, increased incidence of auto-antibodies, and increased infections. Interpretation of this study is limited by factors discussed in Sections 2.2.2.3 and 2.2.2.8. 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).

A limited study in animals also presents evidence for increased susceptibility to *Streptococcus zooepidomicus* (Aranyi et al. 1986). Immune system effects observed in mice exposed orally to trichloroethylene included 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. A study in which a susceptible strain of mice was treated with intraperitoneal injections of trichloroethylene suggests that trichloroethylene can accelerate the autoimmune response (Khan et al. 1995). The immune system may be a sensitive end point for toxic effects from low-level exposure to trichloroethylene; however, no firm conclusions can be drawn from the available information. Additional human and animal studies are needed to better characterize this end point and determine the potential for immunological effects for people exposed to trichloroethylene at hazardous waste sites.

Neurotoxicity. Sufficient human information exists to identify the nervous system as the primary target for acute inhalation trichloroethylene exposure in humans (Nomiyama and Nomiyama 1977; Salvini et al. 1971; Stewart et al. 1970,1974a; Vernon and Ferguson 1969). 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 Vyskocill 956; 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). Several studies of the population in Wobum, 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 did find possible residual cranial nerve damage when comparing the exposed and nonexposed population cohorts (Feldman et al. 1988).

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. Intermediate-duration animal studies via the inhalation route reveal behavioral changes (Albee et al. 1993; Battig and Grandjean 1963; Kulig 1987; Silverman and Williams 1975) and biochemical and histopathological alterations (Haglid et al. 1981). Caution should be used when interpreting the results of these studies, however, because the behavioral changes were not confirmed by biochemical measurements, and biochemical changes were not confirmed by behavioral measurements. Chronic oral animal studies reveal motor deficits (NTP 1988). Thus, the inhalation studies clearly indicate that the nervous system is a target organ, and there is suggestive evidence that exposure via the oral route would also damage this system. A complete battery of neurological tests performed on humans or animals exposed to trichloroethylene via the oral pathway is needed. There are few studies that examine the mechanisms of trichloroethylene-induced effects by the inhalation route; data in this area are needed.

Epidemiological and Human Dosimetry Studies. Several epidemiological studies have been conducted that showed little or no relationship between increased cancer risk and inhalation and dermal exposure to trichloroethylene in the workplace (Axelson 1986; Axelson et al. 1978, 1994; Malek et al. 1979; Shindell and Uhich 1985). There have also been studies of people exposed to a number of solvents including trichloroethylene in the drinking water (ATSDR 1994; Bove et al. 1995; Burg et al. 1995; Byers et al. 1988; Cohn et al. 1994; 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; Kilbum and Warshaw 1992; Waller et al. 1994), neurological effects (ATSDR 1994; Burg et al. 1995; Feldman et al. 1988), an increase in birth defects (Bove et al. 1995; Goldberg et al. 1990; Lagakos et al. 1986a), and cancer (Cohn et al. 1994; Fag&no et al. 1990; Lagakos et al. 1986a). The greatest limitations in these 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, 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 (trichloroethanol and TCA) in the urine and blood (Christensen et al. 1988; Monster and Boersma 1975; Pekari and Aitio 1985b; Wallace et al. 1986a, 1986b, 1986c, 1986d; Ziglio et al. 1984). 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 1996).

Effect. 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. Studies of workers occupationally exposed to trichloroethylene for chronic periods have reported increases in serum levels of liver enzymes (Bauer and Rabens 1974; Schuttman 1970), liver enlargement (Capellini and Grisler 1958; Schuttman 1970), and increased N-acetyl-β-D-glucosaminidase (Brogren et al. 1986). Although these effects are not specific for trichloroethylene exposure, additional research further defining the dose-response relationship 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; Femandez 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. Several investigators are working on PBPK models of trichloroethylene distribution in animals, and studies are under way 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 confiiation. 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. PBPK modeling efforts may help provide much of the needed information.

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 heath effects from animal data. Development and validation of PBPK models is one approach to inter-species comparisons of data.

Methods for Reducing Toxic Effects. The general recommendations for reducing the absorption of trichloroethylene following acute inhalation (HSDB 1994), oral (D'Souza et al. 1985; Withey et al. 1983), dermal, or ocular (HSDB 1994) exposure are well established and have a proven efficacy. 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.

2.10.3 On-going Studies

The National Institute of Environmental Health Sciences is currently sponsoring substantial research into the health effects of trichloroethylene. The relationship between maternal trichloroethylene exposure birth weight is being studied in a human population in Tucson, Arizona. The study is being completed by Dr. S. Rodenbeck at Tulane University (Rodenbeck 1997). Continued research on the possible link between trichloroethylene exposure and human congenital heart defects is being conducted by Dr. S. Goldberg at the University of Arizona, using rat and avian model systems. Reproductive effects in rats, including cell-cell interactions, sperm motility, and myometrial gap junctional communication, are being investigated using both *in vivo* and *in vitro* systems by Dr. R. Loch-Caruso at the University of Michigan. Dr. B. Hoener of the University of California, Berkeley, is continuing development of PBPK models for the disposition and excretion of trichloroethylene and its metabolites in rats and children, while collaboration is on-going with Dr. C. Becker at the same university, with the goal of adapting lead kinetic models to the kinetics and neurotoxicity of trichloroethylene. Dr. M. Philbert of Rutgers University is exploring the effects of trichloroethylene on astrocyte function and fluid homeostasis in the rat brain during postnatal development, and Dr. G. Yost at the University of Utah is studying the mechanisms of trichloroethylene-induced pneumotoxicity in rabbits. Neurobehavioral effects of oral exposure to trichloroethylene in rats are being studied by Dr. Chandra Mehta at Texas Southern University.

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

The chemical formula, structure, synonyms, and identification numbers for trichloroethylene are listed in Table 3-l.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Important physical and chemical properties of trichloroethylene are listed in Table 3-2.

TABLE 3-1. Chemical Identity of Trichloroethylene

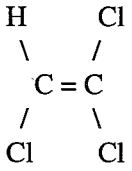
Characteristic	Information	Reference
Chemical name	Trichloroethylene	
Synonym(s)	Acetylene trichloride; 1-chloro-2,2-dichloroethylene; 1,1-dichloro-2-chloroethylene; ethylene trichloride; trichlororide; TCE; 1,1,2-trichloro-ethylene; trichloroethene	IARC 1979
Registered trade name(s)	Algylen; Anamenth; Benzinol; Blacosolv; Blancosolv; Cecolene; Chlorilen; Chlorylea; Chlorylen; Chorylen; Cicosolv; Crawhaspol; Densinfluat; Dow-Tri; Dukeron; Fleck-Flip; Flock Flip; Fluate; Gumalgene; Germalgene; HI-TRI; Lanadin; Lethurin; Narcogen; Narkogen; Narkosoid; NEU-TRI; Nialk; Perma-A-Chlor; Perma-A-Clor; Petzinol; Philex; Threthylen; Threthylene; Tretylene; Triad; Trial; Triasol; Trichloran; Trichloren; Triclene; Tri-Clene; Trielene; Trielin; Triklone; Trilen; Trilene; Triline; Trimar; Triol; TRI-plus; TRI-plus M; Vestrol; Vitran; Westrosol	IARC 1979
Chemical formula	C_2HCl_3	SANSS 1990
Chemical structure		
Identification numbers:		
CAS registry	79-01-6	SANSS 1990
NIOSH RTECS	KX4550000	SANSS 1990
EPA hazardous waste	U228	HSDB 1994
OHM/TADS	7216931	HSDB 1994
DOT/UN/NA/IMCO shipping	UN1710	HSDB 1994
HSDB	133	HSDB 1994
NCI	NCI-C04546	HSDB 1994

TABLE 3-1 (*continued*)

Characteristic	Information	Reference

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

TABLE 3-2. Physical and Chemical Identity of Trichloroethylene

Property	Information	Reference
Molecular weight	131.40	HSDB 1994
Color	Clear, colorless	HSDB 1994
Physical state	Liquid (at room temperature)	HSDB 1994
Melting point	-87.1°C	McNeill 1979
Boiling point	86.7°C	McNeill 1979
Density:		
at 20°C	1.465 g/mL	McNeill 1979
Odor	Ethereal; chloroform-like; sweet	HSDB 1994
Odor threshold:		
Water	No data	
Air	100 ppm	HSDB 1994
Solubility:		
Water at 20°C	1.070 g/L	McNeill 1979
at 25°C	1.366 g/L	Tewari et al. 1982
Organic solvent(s)	Miscible with many common organic solvents (such as ether, alcohol, and chloroform)	McNeill 1979; Windholz 1983
Partition coefficients:		
Log K_{ow}	2.42	Hansch and Leo 1985
Log K_{oc}	2.03–2.66	Garbarini and Lion 1986
Vapor pressure at 25°C	74 mmHg	Mackay and Shiu 1981
Henry's law constant:		
at 20°C	0.020 atm-m^3/mol	Mackay and Shiu 1981
at 25°C	0.011 atm-m^3/mol	Hine and Mookerjee 1975
Autoignition temperature	None	McNeill 1979
Flashpoint	None	McNeill 1979
Flammability limits at 25°C (explosive limits) (volume % in air)	8.0–10.5	McNeill 1979
Conversion factors	-	Verschueren 1983
Air at 20°C	1 mg/m^3 = 0.18 ppm; 1 ppm = 5.46 mg/m^3	-
Water	1 ppm (weight per volume) = 1 mg/L	
Explosive limits	No data	

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

4.1 PRODUCTION

Trichloroethylene is currently produced in the United States using ethylene dichloride (a product of ethylene and chlorine feedstocks) (EPA 1985e). 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.

U.S. production volumes of trichloroethylene in recent years have been reported as follows: 299 million pounds in 1978, 319 million in 1979, 266 million in 1980, 258 million in 1981, and 200 million in 1982 (USITC 1979, 1980, 1981, 1982, 1983). U.S. production demand for trichloroethylene in 1983, 1985, and 1986 is estimated to be 235, 180, and 170 million pounds, respectively (CMR 1983, 1986). The U.S. International Trade Commission (USITC) has not published more recent production statistics because there are only two U.S. manufacturers (HSDB 1994).

The only U.S. manufacturers of trichloroethylene are DOW Chemical in Freeport, Texas, and PPG Industries in Lake Charles, Louisiana (CMR 1986; SRI 1987). These two manufacturers have a combined annual production capacity of 320 million pounds (SRI 1987). Prior to 1982, Ethyl Corporation, Diamond Shamrock, and Hooker Chemical manufactured trichloroethylene (CMR 1983; Mannsville 1992).

The facilities that manufactured or processed trichloroethylene in 1993 are listed in Table 4- 1.

4.2 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

Table 4-1. Facilities That Manufacture or Process Trichloroethylene

State[a]	Number of facilities	Range of maximum amounts on site in thousands of pounds[b]	Activities and uses[c]
AL	12	1-1,000	2, 3, 7, 8, 12, 13
AR	11	1-1,000	8, 9, 11, 12, 13
AZ	4	1-10	12, 13
CA	5	1-10,000	1, 5, 8, 10, 11, 13
CO	1	10-100	12
CT	15	1-100	11, 12, 13
DE	1	100-1,000	13
FL	14	0-100	11, 12, 13
GA	12	1-1,000	8, 12, 13
IA	5	1-10	12, 13
IL	99	0-100,000	1, 4, 8, 9, 10, 11, 12, 13
IN	50	0-10,000	7, 8, 10, 11, 12, 13
KS	12	0-1,000	8, 10, 11, 12, 13
KY	17	1-50,000	1, 3, 7, 10, 12, 13
LA	11	1-10,000	1, 3, 4, 5, 6, 7, 8, 12, 13
MA	36	0-1,000	8, 10, 11, 12, 13
MD	4	1-100	2, 3, 12, 13
ME	2	10-100	13
MI	41	1-1,000	2, 3, 8, 10, 11, 12, 13
MN	28	0-100	11, 12, 13
MO	28	0-1,000	2, 3, 8, 10, 12, 13
MS	6	1-1,000	12, 13
NC	19	0-100	10, 11, 12, 13
NE	10	1-100	11, 12, 13
NH	4	1-100	11, 13
NJ	11	1-1,000	8, 12, 13
NY	55	0-1,000	3, 7, 10, 11, 12, 13
OH	55	0-1,000	8, 10, 11, 12, 13
OK	5	1-100	2, 3, 13
OR	7	0-1,000	11, 12, 13
PA	54	1-1,000	3, 8, 10, 11, 12, 13
PR	1	10-100	13

Table 4-1 (*continued*)

State[a]	Number of facilities	Range of maximum amounts on site in thousands of pounds[b]	Activities and uses[c]
RI	5	0-100	8, 12, 13
SC	12	1-1,000	7, 12, 13
SD	2	10-100	13
TN	14	1-1,000	2, 3, 7, 11, 12, 13
TX	34	1-50,000	1, 3, 4, 5, 6, 7, 8, 10, 12, 13
VA	12	1-1,000	12, 13
VT	3	1-100	11, 13
WA	9	0-100	12, 13
WI	42	0-1,000	8, 10, 11, 12, 13

Source: TRI93 1995

[a]Post office state abbreviations used
[b]Data in TRI are maximum amounts on site at each facility
[c]Activities/Uses:

1. Produce
2. Import
3. For on-site use/processing
4. For sale/distribution
5. As a by-product
6. As an impurity
7. As a reactant
8. As a formulation component
9. As a product component
10. For repackaging only
11. As a chemical processing aid
12. As a manufacturing aid
13. Ancillary or other uses

time period, exports of trichloroethylene fell from 60 million pounds to 18 million pounds. Trends are not easy to predict, however. According to the National Trade Data Bank, imports of trichloroethylene were 3.8 million pounds in 1991, 0.7 million pounds in 1992, and 16.3 million pounds in 1993, while exports were 72.8 million pounds in 1991, 108 million pounds in 1992, and 108 million pounds again in 1993 (NTDB 1994).

4.3 USE

The end-use pattern of trichloroethylene in the United States was estimated as follows (CMR 1986): vapor degreasing of fabricated metal parts, 80%; chemical intermediates, 5%; miscellaneous uses, 5%; and exports, 10%. The most important use of trichloroethylene, vapor degreasing of metal parts, is closely associated with the automotive and metals industries (CMR 1983).

Trichloroethylene is an excellent extraction solvent for greases, oils, fats, waxes, and tars and is used by the textile processing industry to scour cotton, wool, and other fabrics (IARC 1979; Kuney 1986; Verschueren 1983). The textile industry also uses trichloroethylene as a solvent in waterless dying and finishing operations (McNeil1 1979). As a general solvent or as a component of solvent blends, trichloroethylene is used with adhesives, lubricants, paints, varnishes, paint strippers, pesticides, and cold metal cleaners (Hawley 1981; IARC 1979; McNeil1 1979).

Approximately 10 million pounds of trichloroethylene are used annually as a chain transfer agent in the production of polyvinyl chloride (McNeil1 1979). Other chemical intermediate uses of trichloroethylene include production of pharmaceuticals, polychlorinated aliphatics, flame retardant chemicals, and insecticides (Mannsville 1992; Windholz 1983). Trichloroethylene is used as a refrigerant for low-temperature heat transfer (Cooper and Hickman 1982; IARC 1979; McNeil1 1979) and in the aerospace industry for flushing liquid oxygen (Hawley 1981; Kuney 1986).

Various consumer products found to contain trichloroethylene include typewriter correction fluids, paint removers/strippers, adhesives, spot removers, and rug-cleaning fluids (Frankenberry et al. 1987; IARC 1979).

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).

4.4 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 trichloroethylenecontaining 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 1986; McNeil1 1979). 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.

5. POTENTIAL FOR HUMAN EXPOSURE

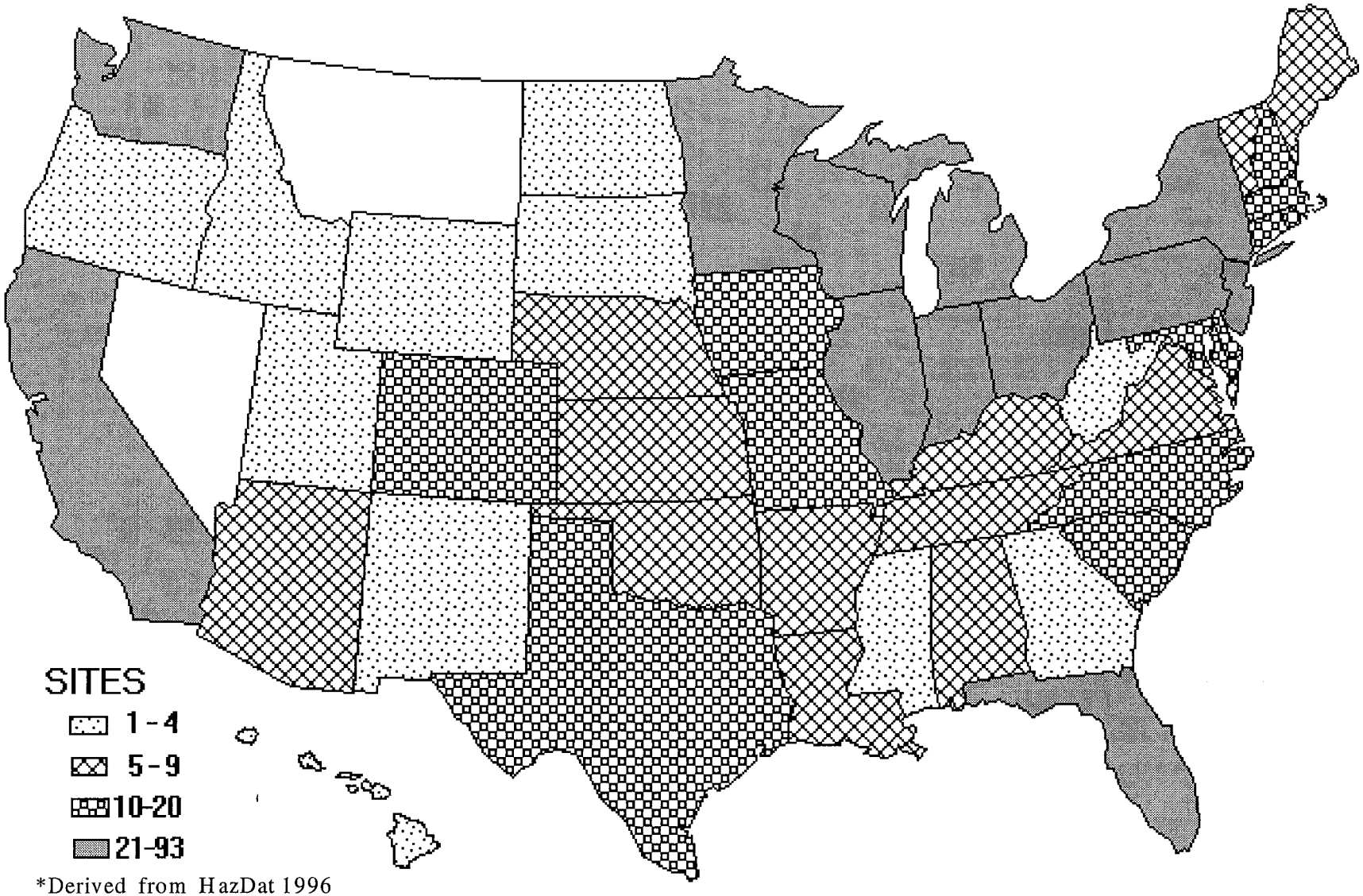
5.1 OVERVIEW

Trichloroethylene has been identified in at least 861 of the 1,428 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 1996). However, the number of sites evaluated for trichloroethylene is not known. The frequency of these sites can be seen in Figure 5-l. Of these sites, 857 are located in the United States and 3 are located in the Commonwealth of Puerto Rico and 1 in the Virgin Islands (not shown).

Most of the trichloroethylane 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.

In general, atmospheric levels are highest in areas of concentrated industry and population and lower in rural and remote regions. 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. Based on available federal and state surveys, between 9% and 34% of the drinking water supply sources that have been tested in the United States may have some trichloroethylene contamination. It should be noted that the amount of trichloroethylene found by chemical analysis is not necessarily the amount that is bioavailable.

FIGURE 5-1. FREQUENCY OF NPL SITES WITH TRICHLOROETHYLENE CONTAMINATION*



*Derived from HazDat 1996

5.2 RELEASES TO THE ENVIRONMENT

5.2.1 Air

According to the Toxic Chemical Release Inventory database (TRI), an estimated total of at least 49 million pounds of trichloroethylene was released to air from manufacturing and processing facilities in the United States in 1988 (TRISS 1990). The level reported in 1993 was 30.2 million pounds (TR1931995). The number of reporting facilities in each state and the ranges within which individual facilities reported their releases are shown in Table 5-l. The TRI 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.

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.

A recently discovered 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 3400 ng/g fresh weightihour, with the higher rates seen in subtropical *Rhodophyta* species. The importance of this source of trichloroethylene cannot be estimated at this time 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. There are too many unknown factors to determine whether this source could be a potential concern as a major source of atmospheric emissions of trichloroethylene in coastal areas.

Table 5-1. Releases to the Environment from Facilities That Manufacture or Process Trichloroethylene

State[b]	Number of Facilities	Reported amounts released in pounds per year[a]						
		Air	Water	Land	Underground injection	Total environment[c]	POTW	Off-site waste transfer
AL	12	1,500-424,000	0-250	0	0	1,500-424,005	0-209	0-186,104
AR	11	2,686-235,200	0	0	0	2,686-235,200	0-5	0-54,176
AZ	4	15,450-55,140	0	0	0	15,450-55,140	0	250-10,200
CA	5	5-13,936	0-1	0	0	5-13,936	0-9	0-3,261
CO	1	6,000	0	0	0	6,000	0	4,000
CT	15	3-94,000	0-148	0	0	3-94,000	0	0-90,999
DE	1	240,000	0	0	0	240,000	0	3,400
FL	14	0-126,000	0	0	0	0-126,000	0-5	0-16,968
GA	12	400-330,303	0	0-750	0	400-330,303	0-550	0-124,827
IA	5	1,363-15,446	0	0	0	1,363-15,446	0-5	0-19,138
IL	99	0-342,748	0-3	0-5	0	0-342,748	0-27,075	0-139,000
IN	50	0-1,126,000	0-250	0	0	0-1,126,000	0-300	0-105,100
KS	12	2,079-514,490	0-5	0	0-460	2,539-514,495	0-5	0-44,345
KY	17	0-216,600	0-5	0	0	0-216,600	0-5	0-39,462
LA	11	3-63,889	0-2,900	0-250	0	3-63,889	0	0-97,000
MA	36	10-176,200	0-5	0	0	10-176,200	0-5	0-248,300
MD	4	9,680-73,100	0	0	0	9,680-73,100	0-2,795	250-20,020
ME	2	8,167-75,375	0	0	0	8,167-75,375	0	0-60,997
MI	41	0-533,400	0-7	0	0	0-533,400	0-250	0-153,206
MN	28	2,640-154,220	0	0	0	2,640-154,220	0-567	0-50,160
MO	28	0-93,620	0-1	0	0	0-93,620	0-250	0-230,653
MS	6	8,900-1,219,813	0	0	0	8,900-1,219,813	0	1,233-12,600
NC	19	0-171,600	0	0	0	0-171,600	0-250	0-3,155,000

Table 5-1 (*continued*)

State[b]	Number of Facilities	Reported amounts released in pounds per year[a]						
		Air	Water	Land	Underground injection	Total environment[c]	POTW	Off-site waste transfer
NE	10	10,639-138,585	0	0	0	10,639-138,585	0-1	0-17,729
NH	4	2,810-88,000	0	0	0	2,810-88,000	0-1	9,021-56,000
NJ	11	0-241,310	0	0	0	0-241,310	0-650	0-120,900
NY	55	4-261,000	0-250	0-600	0	4-261,000	0-9,000	0-66,407
OH	55	0-332,000	0-250	0-6,600	0	0-332,250	0-250	0-209,500
OK	5	14,000-56,005	0	0	0	14,000-56,005	0	0-17,000
OR	7	14,605-186,000	0	0	0	14,605-186,000	0	45-9,548
PA	54	0-201,208	0-500	0-5	0	0-201,713	0-5	0-206,629
PR	1	12,000	0	0	0	12,000	0	6,022
RI	5	500-28,250	0	0	0	500-28,250	0-5	0-32,069
SC	12	500-130,750	0	0	0	500-130,750	0-43	0-150,000
SD	2	255-4,000	0	0	0	255-4,000	0	11,000-11,100
TN	14	6-122,720	0-5	0	0	6-122,720	0-250	0-28,330
TX	34	0-117,683	0-20	0-1	0	0-117,683	0-630	0-40,000
VA	12	2,111-320,255	0	0	0	2,111-320,255	0-250	110-92,585
VT	3	1-1,980	0	0	0	1-1,980	0	1-43,340
WA	9	0-36,278	0	0	0	0-36,278	0-5	0-37,150
WI	42	0-273,300	0-2	0	0	0-273,300	0-5	0-183,590

Source: TRI93 1995

[a]Data in TRI are maximum amounts released by each facility.
[b]Post office state abbreviations used
[c]The sum of all releases of the chemical to air, land, water, and underground injection wells by a given facility

POTW = publicly owned treatment works

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).

5.2.2 Water

According to TRI, an estimated total of at least 13,800 pounds of trichloroethylene was released to water from manufacturing and processing facilities in the United States in 1988 (TRIM 1990). The level reported in 1993 was 5,468 pounds (TR1931995). The number of reporting facilities in each state and the ranges within which individual facilities reported their releases are shown in Table 5-l. The TRI 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.

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).

5.2.3 Soil

According to TRI, an estimated total of at least 21,190 pounds of trichloroethylene was released to land from manufacturing and processing facilities in the United States in 1988 (TRISS 1990). The level reported in 1993 was 8,213 pounds (TR1931995). The number of reporting facilities in each state and the ranges within which individual facilities reported their releases are shown in Table 5-l. The TRI 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.

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).

5.3 ENVIRONMENTAL FATE

5.3.1 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 5.4.2). 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 2.0×10^{-2} atm- m^3 /mol at 20°C suggests that trichloroethylene partitions rapidly to the atmosphere from surface water. The major route of removal of trichloroethylene from water is volatilization (EPA 198%). 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).

Mathematical modeling of trichloroethylene volatilization from a rapidly moving, shallow river (1 meter deep, flowing 1 meter per second, with a wind velocity of 3 meters per second) has estimated its half-life at 3.4 hours (Thomas 1982). 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 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 range from 106 to 460 (Garbarini and Lion 1986). The components of soil organic matter had widely varying affinities for trichloroethylene, with the fats-waxes-resins fraction (K_{oc} = 460) being responsible for stronger adsorption of trichloroethylene. 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 which 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 (Peterson et al. 1994).

A number of groundwater monitoring studies have detected trichloroethylene in groundwater (see Section 5.4.2), 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 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 less than 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 5.4.4), 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.

5.3.2 Transformation and Degradation

5.3.2.1 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), the half-life can be estimated to be 6.8 days. Class and Ballschmiter (1986) state it as between 3 and 7 days. It should be noted that the half-lives determined by assuming first-order kinetics represent the calculated time for loss of the first 50% of trichloroethylene; the time required for the loss of the remaining 50% may be substantially longer.

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 198%). 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).

5.3.2.2 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).

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 1.3×10^6 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 lst 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 (Parsons et al. 1985; Wilson et al. 1986). However, a field study of groundwater at the Lawrence Liver-more 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).

5.3.2.3 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 CNMR) 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 be problematic because a common product is 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 which varied with soil type, temperature, and initial concentration of trichloroethylene (Yagi et al. 1992). The lotus field soils degraded more than 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-Gate11 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; Eng et al. 1991; 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 which 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.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

Monitoring data for trichloroethylene in ambient air in the United States, prior to 1981, were compiled by Brodzinsky and Singh (1982). 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 oftrichloroethylene 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 0.0960.225 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). In these studies, 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 5.3.2.1).

Data gathered from several sites near Niigata, Japan, between April 1989 and March 1992 showed elevated levels of trichloroethylene and other volatile chlorinated hydrocarbons in the winter (Kawata and Fujieda 1993). A rural site in this study had annual mean concentrations between 0.17 and 0.32 ppb, while four industrial sites had mean concentrations between 0.029 and 4.8 ppb. 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).

Data collected from several locations in the city of Hamburg, Germany, showed ambient air concentrations of trichloroethylene ranging from 0.8 to 18.5 µg / m^3 (0.15 to 3.44 ppb) (Bruckmann et al. 1988). A monitoring study in Finland reported levels of 0.27 and 36 µg / m^3 (0.05 and 6.70 ppb) in ambient air from a suburban area and an industrialized area, respectively (Kroneld 1989). No trichloroethylene was detected in samples of rural air in that study.

Some elevated outdoor air levels of trichloroethylene reported 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). Levels between 3.0 and 3.2 μg / m^3 (0.56 ppb and 0.60 ppb) were found at a distance of 0.5-1.5 meters above the surface of a landfill known to contain halogenated volatile organic compounds in Germany (Koenig et al. 1987).

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 trichloroethylene in the air of an indoor university laboratory was 0.008 ppm (8.0 ppb) (Nicoara et al. 1994). Based on the properties of trichloroethylene and a three-compartment model, the levels of trichloroethylene in indoor air have been estimated (McKone 1987). If the tap water contained 1 mg/L, the air in the shower during use was estimated to be 3.3 ppm, while in the rest of the house it was estimated to be 0.02 ppm during the day (7 am-l 1 pm) and 0.0045 ppm during the night (11 pm-7 am).

5.4.2 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 ppt (Sauer 1981). Average levels of 7 ng/L (7 ppt) and 0.3 ppt were found in the northeastern Atlantic (Murray and Riley 1973) and in Liverpool Bay (Pearson and McConnell 1975), respectively.

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).

5. POTENTIAL FOR HUMAN EXPOSURE

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 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 (1 ppb), with a single maximum level of 130 µg /L (130 ppb) (Westrick et al. 1984). 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). In other countries, thirty Canadian drinking water sources were found to contain trichloroethylene levels ranging from <1 to 2 ppb (Otson et al. 1982), and recent drinking water samples from Zagreb, Croatia, contained 0.69-35.9 µg /L (0.69-35.9 ppb) (Skender et al. 1993).

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. Trichlcroethylene 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 Minnesota municipal solid waste landfills at levels ranging from 0.7 to 125 µg /L (0.7-125 ppb) and in groundwater near landfills at levels ranging from 0.2 to 144 µg /L (0.2-144 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 (7,700 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, NH, 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 0.044-180 ppm.

An analysis of the EPA E'TORET 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). 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 levels of 0.008-0.13 µg /L (0.008-0.13 ppb) trichloroethylene were found in the Niagara River and Lake Ontario in 1981 (Strachan and Edwards 1984).

5.4.3 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, NH (Hewitt and Shoop 1994). Concentrations of trichloroethylene in soil from the saturated zone were 0.008-25 mg/kg, while concentrations in the groundwater were 0.044-180 ppm.

5.4.4 Other Environmental Media

Trichloroethylene has been detected in dairy products (milk, cheese, butter) at 0.3-10 µg /kg (0.3-10 ppb), meat (English beef) at 12-16 ppb, oils and fats at O-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 (McConnell et al. 1975). 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 (440-3,600 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 which exceed acceptable limits (Grob et al. 1990). The authors estimated that in order to limit food concentrations of trichloroethylene to 50 µg /kg (the maximum tolerated limit for food halocarbons in Switzerland), the level in surrounding air should not exceed 38.5 µg / m^3 (0.007 ppm). 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 7).

An analysis of six municipal solid waste samples from Hamburg, Germany, revealed levels of trichloroethylene ranging from undetectable to 0.59 mg/kg (Deipser and Stegmann 1994). In a study analyzing automobile exhaust for chlorinated compounds, trichloroethylene was not detected (Hasanen et al. 1979).

5.5 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 ng/L and 0.763 ng/L, 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. The concentrations in drinking water in the city ranged from <0.05 to 22.93 mg/L and from 0.21 to 7.80 µg /L for trichloroethylene and tetrachloroethylene, respectively.

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 mg/day. Average daily water intake of trichloroethylene can be estimated at 2-20 mg/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 to 15,072 ppb) in less than 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 outdoor air, even near major point sources such as chemical plants (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). Post-mortem analyses of human tissue revealed body fat levels of 1.4-32 μg /kg (1.4-32 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 (Frankenberry et al. 1987). 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).

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 (NOES 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 was obtained from degreasing operations, which is the primary industrial use of trichloroethylene. Worker exposure data indicated that exposure is likely to vary, although mean TWA concentrations were generally consistent and usually ranged from ≤50 to 100 ppm (Santodonato 1985). OSHA allows an 8-hour TWA permissible exposure limit of 100 ppm. The 15-minute TWA exposure, which should not be exceeded at any time during a workday, is 300 ppm (OSHA 1993). 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 (Santodonato 1985).

5.6 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).

A survey of 20 brands of typographical correction fluids found that several contained 10% or less 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 (Frankenberry et al. 1987).

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 (McNeil1 1979).

An EPA TEAM (Total Exposure Assessment Methodology) 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.

5.7 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 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.

5.7.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of trichloroethylene are well characterized (HSDB 1994; McNeil1 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 1994). 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 7). 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 chemical release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1992, became available in 1994. This database will be 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). Trichloro-

ethylene is biodegraded in water (Jensen and Rosenberg 1975; Smith and Dragun 1984) and, to a limited extent, in soil (Maymo-Gate11 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; Mtiller et al. 1974; Sato and Nakajima 1978), oral (DeFalque 196 1; D'Souza et al. 1985; Klienfeld 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 Abdul-Rahman 1991; Sato and Nakajima 1978; Steward and Dodd 1964; Tsuruta 1978) exposure. All 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 (Brodzinsky and Singh 1982; 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 19Sl), soil (Hewitt and Shoop 1994; Hunter and Bromberg 1982), and food (Entz and Hollitield 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. This information is necessary for assessing the need to conduct health studies on these populations. 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. More information on exposure levels for populations living in the vicinity of hazardous waste sites is needed for estimating human exposure.

Exposure Registries. A subregistry has been established for trichloroethylene as part of the National Exposure Registry. There are 4,280 persons (along with general health data) enrolled on the subregistry (ATSDR 1994; Burg et al. 1995). This data is part of the public-user data files established and maintained by the Exposure and Disease Registry Branch, Division of Health Studies, ATSDR. The information that is amassed in the National Exposure Registry will facilitate the epidemiological research needed to assess adverse health outcomes that may be related to the exposure to this compound.

5.7.2 On-going Studies

As part of the Third National Health and Nutrition Evaluation Survey (NHANES III), the Environmental Health Laboratory Sciences Division of the National Center for Environmental Health, Centers for Disease Control, will be analyzing human blood samples for trichloroethylene and other volatile organic compour 3s. These data will give an indication of the frequency of occurrence and background levels of these compounds in the general population.

Research on human exposure also includes studies by Dr. J.W. Gillett at Cornell University which model dermal absorption of trichloroethylene and other volatile organic compounds in a simulated shower and bath chamber. The development of a three-dimensional mathematical model for describing exposure from contaminated groundwater of residents living near superfund sites is the focus of work carried out by Dr. C.P. Weisel at Rutgers University. Measurements from a pilot scale soil system are included in the model, along with actual body burden measurements taken from residents, to assess the exposure risk from the transport of trichloroethylene in groundwater through soil and into the basements of homes. Health effects caused by ingestion of foods with fumigant residues, such as trichloroethylene, are being studied in rats by Dr. T. Shibamoto at the University of California, Davis, with the support of the (U.S. Department of Agriculture) USDA.

Several on-going projects are investigating the use of biotechnology to remediate sites contaminated with trichloroethylene. Dr. AK. Shiemke of West Virginia University is working on the isolation of a membrane-bound methane monooxygenase from trichloroethylene-degrading bacteria in order to study its mechanism of action, and related work is being carried out at Iowa State University by Dr. A.A. Dispirito. Reductive dechlorination of chlorinated organic compounds by anaerobes is being studied by Dr. S.H. Zinder at Cornell University. Continuing research on trichloroethylene biodegradation in soil columns under various conditions, including the presence of different cosubstrates and bacterial cultures, is being performed by Dr. K.M. Scow at the University of California, Davis. The potential of a system using methane application to stimulate the *in situ* biodegradation of trichloroethylene in groundwater by methanotrophs is being investigated by Dr. W.J. Jewel1 of Cornell University. A similar approach exploiting the nonspecific oxygenase activity of some nitrifying bacteria induced by ammonia and other water-soluble compounds is being studied by Dr. K.A. Sandbeck at Geomicrobial Technologies, Inc. Dr. H. Bohn at the University of Arizona is conducting USDA-supported research to discover the optimal redox conditions for trichloroethylene degradation in soil.

Nonbiological methods for removal of trichloroethylene from water are also being studied. These include the use of a hollow fiber membrane contactor (Dr. AK. Zander, Clarkson University), photocatalysis by solar or artificially irradiated semiconductor powders (Dr. G. Cooper, Photocatalytics, Inc.), and micellar-enhanced ultrafiltration (Dr. B.1. Roberts, Surfactant Associates, Inc.).

6. 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 may be included that modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

6.1 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). Trichloroethylene and/or its metabolites have been detected in exhaled air, blood, urine, breast milk, and tissues. Details on sample preparation, analytical method, and sensitivity and accuracy of selected methods are provided in Table 6- 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®

TABLE 6-1. 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 trichloroethylene and trichloroethanol)	5 ppb (trichloroethylene); 2 ppb (trichloroethanol)	NR	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	Digested with H_2SO_4: dimethylsulfate at 60°C for 4 hours; headspace gas injected into GC	GC/ECD (trichloroethylene, trichloroethanol, and trichloroacetic acid)	3 ppb (trichloroethylene); 60 ppb (trichloroethanol); 30 ppb trichloroacetic acid)	NR	Monster and Boersma 1975
Blood	Thermally decarboxylated; subjected to static headspace analysis	GC/ECD (for metabolite trichloroacetic acid)	2 ppb	101–109	Ziglio et al. 1984

TABLE 6-1. Analytical Methods for Determining Trichloroethylene in Biological Materials (*continued*)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood	Enzyme hydrolysis of sample; decarboxylation of trichloroacetic acid; headspace gas analyzed	GC/ECD	20 ppb	95 (trichloroethanol); 102 (trichloroethanol); 94 (trichloroacetic acid)	Christensen et al. 1988
Blood, plasma, and serum	Sample in sealed vial subjected to static headspace analysis	GC/ECD	100 ppb	NR	Ramsey and Flanagan 1982
Urine	Thermally decarboxylated; reacted with pyridine	Spectrophotometry (for metabolite trichloroacetic acid)	<800 ppb	93.5	Pekari and Aitio 1985a
Urine	Enzyme hydrolysis of sample; decarboxylation of trichloroacetic acid; headspace gas analyzed	GC/ECD	20 ppb	96 (trichloroethanol); 98 (trichloroacetic acid)	Christensen et al. 1988

TABLE 6-1. Analytical Methods for Determining Trichloroethylene in Biological Materials (*continued*)

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 trichloroethanol)	75 ppb	98.2	Pekari and Aitio 1985b
Tissue	Mixed with a proteolytic enzyme; incubated at 65°C; headspace gas analyzed	GC/ECD	NR	NR	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
Human milk	Purged warm; trapped in Tenax®-GC; thermally desorbed	HRGC/MS	Qualitative identification	NR	Pellizzari et al. 1982

ECD = electron capture detector; GC = gas chromatography; HRGC = high-resolution gas chromatography; H_2SO_4 = sulfuric acid; MS = mass spectrometry; NR = not reported

bag into a gas chromatograph equipped with an ECD (Monster and Boersma 1975). Sensitivity was better with GC/MS, but precision 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-B-glucuronide has been done primarily by headspace GC/ECD (Christensen et al. 1988). Trichloroethanol-pglucuronide in the samples was first hydrolyzed to trichloroethanol by β-glucuronidase, then TCA was 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).

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.

6.2 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). Preconcentration of samples is usually done by sorption on a solid sorbent for air 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 6-2.

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. The detection and measurement of trichloroethylene in air can also be adequately performed using infrared spectrometry instead of GC (Xiao et al. 1990).

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; EPA 1982b, 1982c; Otson and Williams 1982; Wallace et al. 1986a, 1986c, 1986d). The limit of detection is in the subppb range for halogen-specific detectors (APHA 1985; EPA 1982b, 1982c) and in the low-ppb range for MS (EPA 1982b). 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 Eenahan 1984).

TABLE 6-2. Analytical Methods for Determining Trichloroethylene in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Collected in stainless steel canister; preconcentrated in cooled adsorbent; thermally desorbed	GC/ECD	1 ppt	NR	Makide et al. 1979
Air	Adsorbed on Tenax®-GC thermally desorbed to on-column cold trap; heat-released	HRGC/MS	1.9 ppt	NR	Krost et al. 1982
Air	Collected in stainless steel canister; preconcentrated by cryogenic trapping; thermally desorbed	GC/ECD	0.3 ppt	NR	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
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

TABLE 6-2 (*continued*)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water	Purged and trapped on coconut charcoal/Tenax®/silica gel; thermally desorbed	GC/HSD	0.12 ppb	106	EPA 1982b
Water	Equilibrated in sealed vial at room temperature; headspace gas injected into GC	GC/ECD	.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	.05 ppb	50–90	Wallace et al. 1986a
Water	Sample directly injected	GC/UV	1 ppb	39	Motwani et al. 1986
Soil	Equilibrated in sealed vial; headspace gas injected into GC	GC/PID	100 ppb	NR	Hewitt et al. 1992

TABLE 6-2 (*continued*)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Soil	Equilibrated in sealed vial; headspace gas injected into GC	GC/FID	NR	80	Pavlostathis and Mathavan 1992
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	NR	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
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

TABLE 6-2 (*continued*)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
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

[a]Sample is air from an environmental chamber containing the building material or consumer product.

ECD = electron capture 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; NR = not reported; PID = photoionization detection; UV = ultraviolet detection

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).

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 (Boekhold et al. 1989; Entz and Hollifield 1982; EPA 1982b). 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).

6.3 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 the 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.

6.3.1 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. Existing methods for measuring biomarkers of effect are the same as those for exposure. These methods are sensitive for measuring levels of trichloroethylene and its metabolites at which health effects have been observed, for example, in workers known to be overexposed to trichloroethylene. Improved methods of tissue analysis, giving greater sensitivity and reproducibility, would also 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 β_2-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 β_2-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 6-l). 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.

6.3.2 On-going Studies

The Environmental Health Laboratory Sciences Division of the National Center for Environmental Health, Centers for Disease Control and Prevention, is developing methods for the analysis of trichloroethylene and other volatile organic compounds in blood. 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.

A method of monitoring chemicals expired by rats exposed to trichloroethylene and other fumigants is being developed at the University of California, Davis. Investigators plan to determine possible relationships between chemicals produced and internal damage produced by exposure to trichloroethylene. Researchers at New York University Medical Center are investigating methods for detecting human chemical exposure *in vivo* using noninvasive sampling procedures.

7. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding trichloroethylene in air, water, and other media are summarized in Table 7- 1.

Trichloroethylene is on the list of chemicals appearing in “Toxic Chemicals Subject to Section 3 13 of the Emergency Planning and Community Right-to-Know Act of 1986” (EPA 1987i, 19%).

ATSDR has derived an acute-duration inhalation MRL of 2 ppm with an uncertainty factor of 30 based on neurological effects in humans (Stewart et al. 1970) and an intermediate-duration inhalation MRL of 0.1 ppm with an uncertainty factor of 300 based on neurological effects in rats (Arito et al. 1994a). An acute-duration oral MRL of 0.2 mg/kg/day with an uncertainty factor of 300 was derived based on developmental effects in mice (Fredriksson et al. 1993).

The oral reference dose (RfD) for trichloroethylene is currently under review by an EPA Workgroup (IRIS 1996). No inhalation reference concentration (RfC) has been derived (IRIS 1996). The National Center for Environmental Assessment, EPA has begun an effort to reassess the health risks associated with trichloroethylene.

In 1988, the Scientific Advisory Board for the EPA offered an opinion that the weight-of-evidence was on a C-B2 continuum (possible-probable human carcinogen). The cancer classification is currently under review by EPA (IRIS 1996).

Trichlorethylene has been nominated for listing in the National Toxicology Program (NTP) 9th Report on Carcinogens. Evaluation of this substance by the NTP review committees is ongoing (NTP 1997)

IARC designates trichloroethylene as Group 2A, or probably carcinogenic to humans (IARC 1995).

Table 7-1. Regulations and Guidelines Applicable to Trichloroethylene

Agency	Description	Information	References
INTERNATIONAL			
IARC	Carcinogenic classification	Group 2[a]	IARC 1995
WHO	TWA	135 mg/m^3	WHO 1981
	Ceiling limit value (15 minutes)	1000 mg/m^3	WHO 1981
	Drinking water guidance level based on a carcinogenic end point	30 µg/L	WHO 1984
NATIONAL			
Regulations:			
a. Air:			
OSHA	PEL TWA	100 ppm	OSHA 1993
	STEL	300 ppm	OSHA 1993
b. Water:			
EPA ODW	MCL in drinking water (final)	0.005 mg/L	IRIS 1996
	Regulated under SDWA of 1986	Yes	FSTRAC 1990
c. Food:			
FDA	Indirect food additive for use only as a component of adhesives	Yes	FDA 1977a (21 CFR 175.105), 1977b
d. Other:			
EPA OERR	Reportable quantity	1000 pounds	EPA 1985a (40 CFR 302), 1986a (40 CFR 117), 1987h
	Proposed	100 pounds	
EPA OSW	Designated as a hazardous substance under Section 311(b)(2)(A) of the Federal Water Pollution Control Act	Yes	EPA 1978a (40 CFR 116.4), 1978b
	Designated as a toxic pollutant under Section 307(a)(1) of the Federal Water Pollution Control Act	Yes	EPA 1979c
	When used as a spent solvent, listed as a hazardous waste from nonspecific sources	Yes	EPA 1981c (40 CFR 261.13); EPA 1981e
	Listing as a hazardous waste: Column bottoms or heavy ends from the combined production of PCE and TCE	Yes	EPA 1981d (40 CFR 261.32); EPA 1981e

Table 7-1. Regulations and Guidelines Applicable to Trichloroethylene (continued)

Agency	Description	Information	References
NATIONAL (contd.)			
	Listing as a hazardous waste: Discarded commercial chemical products off-specification species, container residues, and spill residues thereof	Yes	EPA 1981b (40 CFR 261.33); EPA 1980b
	Listing as a Hazardous Constituent	Yes	EPA 1988a (40 CFR 261, Appendix VIII); EPA 1988b
	Listing as hazardous air pollutant under Section 112(b)(1) of the Clean Air Act	Yes	CAAA 1990
	Groundwater monitoring requirement	Yes	EPA 1987b (40 CFR 264, Appendix IX); EPA 1987f
EPA OTS	Toxic Chemical Release Reporting; Community Right-to-Know	Yes	EPA 1988c (40 CFR 372); EPA 1987i
Guidelines:			
a. Air:			
NIOSH	TWA	Lowest concentration feasible	NIOSH 1994b
ACGIH	TLV TWA	50 ppm	ACGIH 1996
	STEL	100 ppm	ACGIH 1996
	Carcinogenic classification	Group A5[b]	ACGIH 1996
	Biological Exposure Index:		ACGIH 1996
	In urine at end of workweek	100 mg/L	
	In urine at end of shift at end of workweek	300 mg/L	
		4 mg/L	
	Free TCE in blood at end of shift at end of workweek	0.5 ppm	
	In end-exhaled air prior to last shift of workweek		
b. Water:			
EPA ODW	MCLG	0	EPA 1989b
	MCLG Category	I	EPA 1987g
	Health Advisories	No data	IRIS 1996
	Drinking Water Equivalent Level	0.26 mg/L	EPA 1987c

Table 7-1. Regulations and Guidelines Applicable to Trichloroethylene (continued)

Agency	Description	Information	References
NATIONAL (contd.)			
NAS	SNARL		
	24 hours	105 mg/L	NAS 1980
	7 days	15 mg/L	
EPA OWRS	Ambient Water Quality Criteria for Protection of Human Health[c]		EPA 1991
	Ingesting water and organisms:		
	10^{-5}	27 µg/L	
	10^{-6}	2.7 µg/L	
	10^{-7}	0.27 µg/L	
	Ingesting organisms only:		
	10^{-5}	807 µg/L	
	10^{-6}	80.7 µg/L	
	10^{-7}	8.07 µg/L	
c. Other:			
EPA	RfD (oral)	Under review	IRIS 1996
	Carcinogenic Classification[d]	Under review	IRIS 1996
	Unit risk (air)	Under review	IRIS 1996
	Unit risk (water)	Under review	IRIS 1996
STATE			
Regulations and Guidelines:			
a. Air:			
	Acceptable Ambient Air Concentration (70 years)		NATICH 1994
Arizona	(1 hour)	11000 µg/m^3	
	(24 hours)	280 µg/m^3	
	(1 year)	0.76 µg/m^3	
	(70 years)	0.05 µg/m^3	
Connecticut	(8 hours)	1350 µg/m^3	
Florida	(8 hours)	2700 µg/m^3	
	(1 year)	0.77 µg/m^3	
Illinois	(1 year)	0.588 µg/m^3	
Indiana	(8 hours)	2670 µg/m^3	
	(1 year)	0.59 µg/m^3	
Kansas	(1 year)	0.588 µg/m^3	
Louisiana	(1 year)	58.8 µg/m^3	
Maine	(1 year)	0.20 µg/m^3	
Michigan	(1 year)	0.60 µg/m^3	

Table 7-1. Regulations and Guidelines Applicable to Trichloroethylene (continued)

Agency	Description	Information	References
STATE (contd.)			
North Carolina	(1 year)	0.059 mg/m^3	
North Dakota	(1 hour)	10700 µg/m^3	
North Dakota	(8 hours)	2700 µg/m^3	
Nevada	(8 hours)	6430 µg/m^3	
New York	(1 year)	900 µg/m^3	
Oklahoma	(24 hours)	13400 µg/m^3	
Pennsylvania	(1 year) (1 year) (1 year)	76.9 µg/m^3 6840 µg/m^3 1200 ppb	
Rhode Island	(1 year)	0.30 µg/m^3	
South Carolina	(24 hours)	6750 µg/m^3	
South Dakota	(8 hours)	2700 µg/m^3	
Texas	(30 minutes) (1 year)	1350 µg/m^3 135 µg/m^3	
Vermont	(1 year)	0.42 µg/m^3	
Virginia	(24 hours)	4500 µg/m^3	
Washington	(1 year)	0.80 µg/m^3	
Wisconsin	(24 hours)	6480 µg/m^3	
Kentucky	Significant emission levels of toxic air pollutants	0.06889 pounds/ hour	NREPC 1986 (401 KAR 63.021)
New Jersey	Emissions are prohibited unless equipment or operation is registered within 6 months of effective date	Yes	CELDS 1990
	Emissions are prohibited from source operations unless they are:		CELDS 1990
New Jersey (contd.)	Above grade	>40 feet	
	Higher than any human use area	>20 feet	
	Occupancy within	50 feet	
	Directed vertically upward at a discharge velocity of:	>3600 feet/ minute	

Table 7-1. Regulations and Guidelines Applicable to Trichloroethylene (continued)

Agency	Description	Information	References
STATE (contd.)			
Wisconsin	Hazardous air contaminants with acceptable ambient concentrations: Emission points <25 feet Emission points ≥25 feet	 22.485 pounds/hour 94.4160 pounds/hour	WAC 1988
b. Water:	Drinking water quality guidelines and standards		FSTRAC 1990
Alabama		5 µg/L	
Arizona		3.2 µg/L	
California		5 µg/L	
Connecticut		5 µg/L	
Florida		3 µg/L	
Maine		5 µg/L	
Minnesota		31.2 µg/L	
New Hampshire		2.8 µg/L	
New Jersey		1 µg/L	
Rhode Island		5 µg/L	
Vermont		5 µg/L	
	MCL for Drinking Water		CELDS 1990
Alabama		0.005 mg/L	
North Dakota		0.005 mg/L	
Puerto Rico		50 ppb	
Texas		0.005 mg/L	
Oklahoma	MAL for Drinking Water	0.005 mg/L	CELDS 1990
Utah	Groundwater Quality Standards	0.005 mg/L	CELDS 1990
Washington, D.C.	Water Quality Standards		CELDS 1990
	Class C waters protected for aquatic life, waterfowl, shore birds, and water-oriented wildlife	1000 mg/L	

Table 7-1. Regulations and Guidelines Applicable to Trichloroethylene (continued)

Agency	Description	Information	References
STATE (contd.)			
	Class D waters protected for use as a raw water source for public water supply	3.0 mg/L	
Wisconsin	Public Health Groundwater Quality Standards Enforcement Standard Preventative Action Limit	 1.8 µg/L 0.18 µg/L	WAC 1985
	Human cancer criteria		DNR 1987
	Public water supply:		
	Warm water sport fish communities	5 µg/L	
	Cold water communities	5 µg/L	
	Great Lake communities	5 µg/L	
	Nonwater supply:		DNR 1987
	Warm water sport fish communities	360 µg/L	
	Cold water communities	110 µg/L	
	Warm water forage and limited forage fish communities and limited aquatic life	3600 µg/L	

[a] Group 2A: Trichloroethylene is probably carcinogenic to humans.
[b] Group A5: Not suspected as a human carcinogen. Trichloroethylene is not suspected to be a human carcinogen on the basis of properly conducted epidemiologic studies in humans.
[c] Because of its carcinogenic potential, the EPA-recommended concentration for trichloroethylene in ambient water is zero. However, because attainment of this level may not be possible, levels that correspond to upper-bound incremental lifetime cancer risks of 10^{-5}, 10^{-6}, and 10^{-7} are estimated.
[d] The carcinogen classification has been withdrawn following further review by the Carcinogenicity Risk Assessment Verification Endeavor (CRAVE) workgroup. Trichloroethylene was classified as B2, a probable human carcinogen.

ACGIH = American Conference of Governmental Industrial Hygienists; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; IARC = International Agency for Research on Cancer; MAL = Maximum Allowable Level; MCL = Maximum Contaminant Level; MCLG = Maximum Contaminant Level Goal; NAS = National Academy of Sciences; NIOSH = National Institute for Occupational Safety and Health; ODW = Office of Drinking Water; OERR = Office of Emergency and Remedial Response; OSHA = Occupational Safety and Health Administration; OSW = Office of Solid Wastes; OTS = Office of Toxic Substances; OWRS = Office of Water Regulations and Standards; PCE = Tetrachloroethylene; PEL = Permissible Exposure Limit; RfD = Reference Dose; SDWA = Safe Drinking Water Act; SNARL = Suggest No-Adverse-Response Level; STEL = Short Term Exposure Limit; TCE = Trichloroethylene; TLV = Threshold Limit Value; TWA = Time-Weighted Average; WHO = World Health Organization

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9. GLOSSARY

Acute Exposure -- Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

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 a 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.

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.

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 populatioand its appropriate control.

Carcinogen -- A chemical capable of inducing cancer.

Ceiling Value -- A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure -- Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

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.

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 occurred. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

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.

Immediately Dangerous to Life or Health (IDLH) -- The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

Intermediate Exposure -- Exposure to a chemical for a duration of 15-364 days, as specified in the Toxicological Profiles.

Immunologic Toxicity -- The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

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 which 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 is expected to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50}) -- The dose of a chemical which 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 dose 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.

Malformations -- Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level -- An estimate of daily human exposure to a dose of a chemical that is likely to be without an appreciable risk of adverse noncancerous effects over a specified duration of exposure.

Mutagen -- A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity -- The occurrence of adverse effects on the nervous system following exposure to chemical.

No-Observed-Adverse-Effect Level (NOAEL) -- The dose of 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.

Permissible Exposure Limit (PEL) -- An allowable exposure level in workplace air averaged over an 8-hour shift.

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).

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 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 CERCLA. Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity -- The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Short-Term Exposure Limit (STEL) -- The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

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) -- A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-Weighted Average (TWA) -- An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose (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.

Uncertainty Factor (UF) -- A factor used in operationally deriving the RfD 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 LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX A
ATSDR MINIMAL RISK LEVEL

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Super-fund Amendments and Reauthorization Act (SARA) [Pub. L. 99-4991, 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 hJRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1-14 days), intermediate (15-364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. h4RLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth

defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agencywide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL WORKSHEETS

Chemical Name: Trichloroethylene
CAS Number: 79-01-6
Date: July 1997
Profile Status: Final
Route: [X] Inhalation [ ] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 17
Species: human

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

Reference: Stewart et al. 1970

Experimental design: Six humans (sex unspecified) were exposed to 200 ppm trichloroethylene for 5 days, 7 hours/day in a confined chamber. Previous experiments had shown no effects at lower concentrations. No controls were used in this study.

Effects noted in study and corresponding doses: Mild subjective neurological effects (eye and throat irritation, headache, fatigue, drowsiness) were reported at 200 ppm (LOAEL). No objective effects, as measured by dexterity and coordination tests, were seen. However, 50% of the subjects reported that the neurobehavioral tests required greater mental effort for them to perform.

Dose and end point used for MRL derivation: 200 ppm for mild subjective neurological effects

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 3 for use of a minimal LOAEL
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose?
If so, explain:

If an inhalation study in animals, list the conversion factors used in determininp human eauivalent dose:
Calculations: 200 ppm X 7/24 hr X l/30 UF = 1.94 ppm.

Other additional studies or pertinent information which lend sunnort to this MRL: Rats exposed to 1,000 ppm trichloroethylene for 3 days showed disturbed sleep cycles (Arito et al. 1993). Rats exposed to 250 ppm for less than 8 hours showed decreased electric shock avoidance and frequency of Skinner box lever press (Kishi et al. 1991). Humans exposed to 27 ppm trichloroethylene for up to 4 hours noted drowsiness,

and headache was reported at 81 ppm (Nomiyama and Nomiyama 1977). Humans exposed for 8 hours to 110 ppm showed decreased performance on perception, memory, reaction time, and manual dexterity tests (Salvini et al. 1971).

APPENDIX A

Chemical Name: Trichloroethylene
CAS Number: 79-01-6
Date: July 1997
Profile Status: Final
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 50
Species:rat

Minimal Risk Level: 0.1 mg/kg/day [X] ppm

Reference: Arito et al. 1994a

Experimental design: Five male JCL-Wistar rats per group, were exposed by inhalation to 0, 50, 100, or 300 ppm for 6 weeks, 5 days per week, 8 hours per day.

Effects noted in study and corresponding doses: Decreased post-exposure heart rate and slow wave sleep were observed at 50 ppm (less serious LOAEL). Decreased wakefulness was observed during the exposures. Disturbed heart rates and sleep patterns (sleep apnea) have been seen in human exposures to organic solvents as well.

Dose and end point used for MRL derivation: 50 ppm for neurological effects: decreased wakefulness during the exposure; decreased slow wave sleep after the exposures.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 10 for use of a LOAEL
[X] 3 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? No.
If so, explain:

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

V_A male Wistar rat = 0.23 m^3 /day, BW = 0.217 kg
V_A human = 20 m^3 /day, BW = 70 kg

Calculations: 50 ppm X 8/24 hours X 517 days X (0.23 m^3 /day/0.217 kg)/(20 m^3 /day/70 kg)X l/300 UF = 0.147 ppm.

Other additional studies or pertinent information which lend support to this MRL:

Rats exposed to 1,000 ppm TCE for 3 days had disturbed sleep cycles (Atito et al. 1993). Rats exposed to 1,000 ppm for 18 weeks showed increased latency in visual discrimination tasks (Kulig 1987). Sleep apnea has been observed in humans exposed to organic solvents (Edling et al. 1993; Monstad et al. 1987,1992; Wise et al. 1983). Cardiac arrhythmia has been observed in humans exposed to trichloroethylene vapor (Dhuner et al. 1957; Hewer 1943; Milby 1968; Pembleton 1974; Thiersten et al. 1960).

Chemical Name: Trichloroethylene
CAS Number: 79-01-6
Date: August 1997
Profile Status: Final
Route: [ ] Inhalation [x] Oral
Duration: [x] Acute [ ] Intermediate [ ] Chronic
Graph Key: 19
Species: mouse

Minimal Risk Level: 0.2 [X] mg/kg/day [ ] ppm

Reference: Fredriksson et al. 1993

Experimental design: Groups of 12 male NMRI mouse pups were treated by gavage with 0,50, or 290 mg/kg/day trichloroethylene in a 20% peanut oil emulsion. The pups were treated for 7 days beginning at 10 days of age. The doses selected did not sedate the mice. At 17 and 60 days of age behavior was tested. The tests were performed between 8 am-12 pm. Locomotion, rearing, and total activity were measured in an automated device with high and low level infrared beams.

Effects noted in study and corresnonding doses: During the treatment period the mice did not show any symptoms of toxicity. There were no effects on body weight gain. No effects on spontaneous motor behavior were observed at 17 days of age. On postnatal day 60, mice treated at both 50 and 290 mg/kg/day exhibited a significantly reduced (p4.01) rearing rate (raising front legs, resting on haunches) compared to controls. The effect was observed during the first two 20 minute test period, but not during the last 20 minute test periods when rearing rate in the controls was greatly reduced. A dose-response relationship was not apparent.

Dose and end noint used for MRL derivation: 50 mg/kg/day for decreased rearing observed in 60-day-old mice that were treated at 10-16 days of age.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 3 for human variability (pups represent a sensitive subpopulation; the factor of 3 accounts for variation in the metabolism of trichloroethylene which was shown to be less than lofold in an *in vitro* study [Lipscomb et al. 19971)

Calculations: 50 mg/kg/day X l/300 UF = 0.2 mg/kg/day.

Was a conversion used from ppm in food or water to a me/bodv weipht dose?

If so, explain: No.

If an inhalation study in animals, list the conversion factors used in determininp human eauivalent dose:

Other additional studies or nertinent information which lend supportto this MRL: Additional studies have reported developmental effects in rodents exposed to trichloroethylene. Following exposure of rats on gestation days 6-19, decreased litter size (Narotsky and Kavlock 1995), and increased micro- or anophthahnia (Narotsky and Kavlock 1995; Narotsky et al. 1995) were observed in the offspring at 1,125 mg/kg/day, but not at 844 mg/kg/day (Narotsky et al. 1995).

In a series of intermediate-duration studies of pups from rats treated with tichloroethylene in drinking water at a dose of approximately 37 mg/kg/day 14 days before mating, throughout gestation and through weaning, developmental neurotoxicity was observed (Isaacson and Taylor 1989; Noland-Gerbec et al. 1986; Taylor et al. 1985). The effects observed included a decrease in the number of myelinated fibers in the hippocampus (Isaacson and Taylor 1989), decreased uptake of glucose by the brain (Noland-Gerbec et al. 1986), and increased exploratory behavior (Taylor et al. 1985). Rat pups from dams exposed to 300 mg/kg/day trichloroethylene in drinking water showed increased time for grid traversal (open field activity) when tested at 21 days of age, but not at 45 days of age (NTP 1986b).

In addition to developmental neurological effects in animals exposed to trichloroethylene during gestation, cardiac defects have been reported. Heart abnormalities were observed in rats treated with trichloroethylene in the drinking water at 1.5 and 1100 mg/L for 3 months before mating, throughout gestation through weaning (Dawson et al. 1993). Because of errors in recording drinking water intake, accurate mg/kg/day doses could not be developed for this study.

Human epidemiology studies of persons exposed to trichloroethylene in drinking water also provide limited support that trichloroethylene is a developmental toxicant. However, none provide sufficient information on exposure levels. In a study that examined the association between drinking water contaminants and birth outcome in New Jersey, central nervous system defects, neural tube defects, and oral cleft defects were associated with trichloroethylene exposure (Rove et al. 1995). In the Tucson Valley in Arizona, an association between trichloroethylene contaminated drinking water and congenital cardiac malformations was reported (Goldberg et al. 1990). However, interpretation of this finding is limited because exposures to trichloroetbylene in the study population were ill-defined as to the amount and duration of exposure. When compared to rates from the National Health Interview Survey, a statistically significant increase in speech and hearing impairment was reported in children aged 9 years or younger in the ATSDR Trichloroethylene Subregistry (Burg et. al 1995). Birth defects other than cardiac anomalies (defects of the eye, ear, and central nervous system, chaonal atresia, hypospadias/congenital chordee, oral clefts) were observed in a population study conducted by the Massachusetts Department of Health (MDPH 1994). In addition, an association between exposure to trichloroethylene and low birthweight was one of the preliminary findings in an interim report on adverse birth outcomes for a population living at Camp LeJeune, North Carolina (ATSDR 1997). However, interpretation of these data are limited by the small sample size and further analyses are ongoing. Taken together, the body of evidence from reports in humans and in animals strongly suggests that birth defects from exposures to trichloroethylene may be a concern. However, available data do not provide firm conclusions on the dose-response relationship nor a complete understanding of the specific adverse birth outcomes that might result nom exposures.

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

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1,2-2, and 2-3) and figures (2-l and 2-2) 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, minimal risk levels (MI&s) 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 No-Observed-Adverse- Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 2-l and Figure 2-l are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-1

(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. When sufficient data exists, 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 Table 2- 1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-l) and oral (LSE Figure 2-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

(2) Exposure Period Three exposure periods - acute (less than 15 days), intermediate (15-364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 " 18r" data points in Figure 2-l).

(5) Species The test species, whether animal or human, are identified in this column. Section 2.5, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 2.3, "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 regimen 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 1,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 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,l systemic effect (respiratory) was investigated.

(8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote *B").

(9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint 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 8 of the profile.

(11) CEL Cancer Effect Level (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 the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Figure 2-1

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 intermediate and chronic 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, 18r NOAEL is the critical endpoint for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. 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) COL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level 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 Croup's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q1*).

(19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1 → **TABLE 2-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

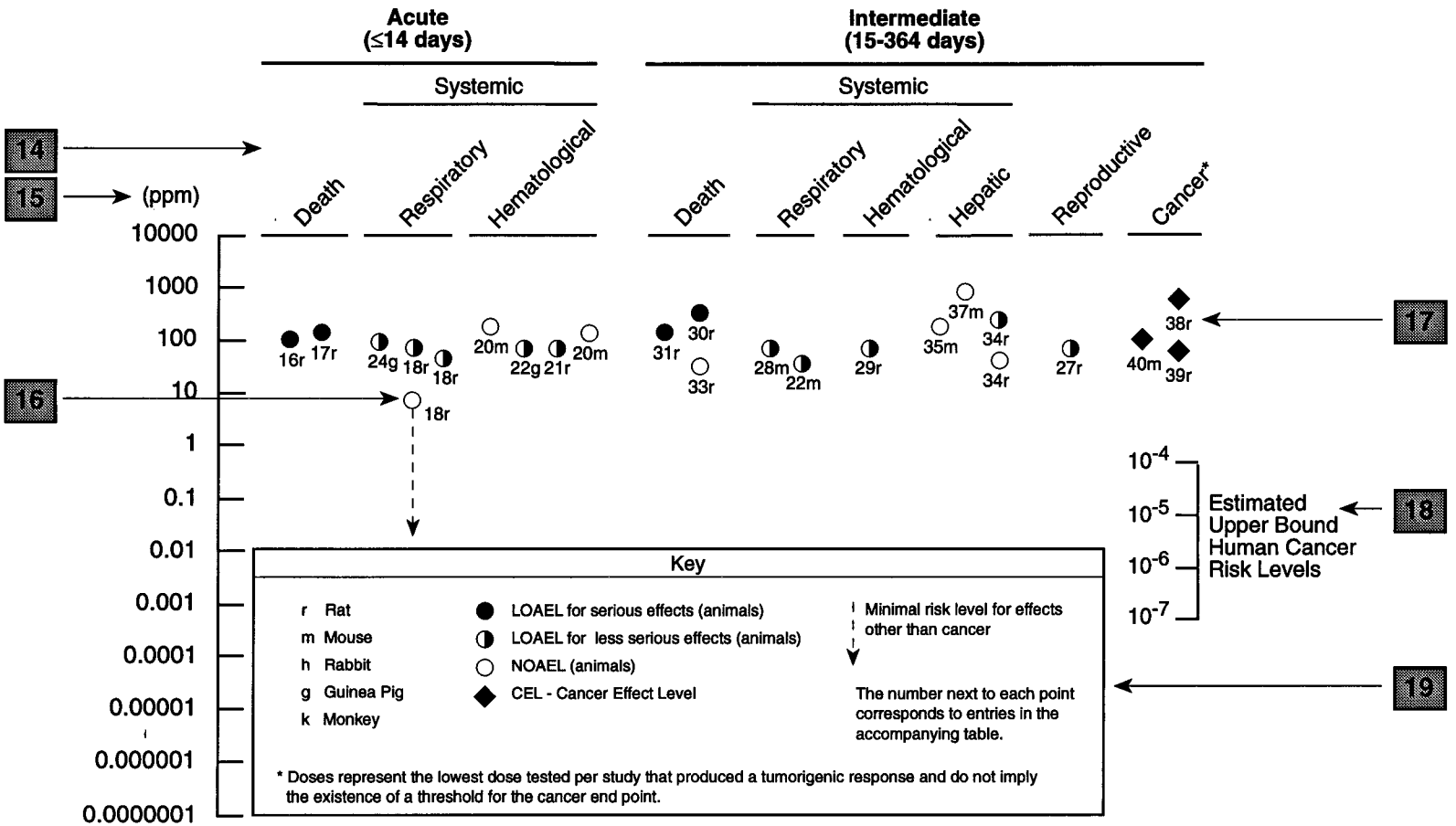
Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE						
	5	6	7	8	9	10
3 → Systemic	↓	↓	↓	↓	↓	↓
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3 [b]	10 (hyperplasia)	Nitschke et al. 1981
CHRONIC EXPOSURE						
					11	
Cancer					↓	
38	Rat	18 mo 5d/wk 7hr/d			20 (COL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5d/wk 6hr/d			10 (COL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5d/wk 6hr/d			10 (COL, lung tumors, hemangiosarcomas)	NTP 1982

[a] The number corresponds to entries in Figure 2-1.

12 → [b] divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

13 → **Figure 2-1. Levels of Significant Exposure to [Chemical X] – Inhalation**



Chapter 2 (Section 2.5)

Relevance to Public Health

The Relevance to Public Health section 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 section covers end points in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, 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 section. If data are located in the scientific literature, a table of genotoxicity information is included.

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 (MIL) 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 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MI&s) 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. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2.5, “Relevance to Public Health,” contains basic information known about the substance. Other sections such as 2.7, “Interactions with Other Substances,” and 2.8, “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 the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

To derive an h4RL, ATSDR generally selects the most sensitive endpoint 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 endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest 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 (UP) 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 LSE Tables.

APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
AML	acute myeloid leukemia
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BEI	Biological Exposure Index
BSC	Board of Scientific Counselors
C	Centigrade
CDC	Centers for Disease Control
COL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CNS	central nervous system
d	day
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
F	Fahrenheit
F_1	first filial generation
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
fpm	feet per minute
ft	foot
FR	*Federal Register*
g	gram
GC	gas chromatography
gen	generation
HPLC	high-performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health

APPENDIX C

IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	trans,trans-muconic acid
mCi	millicurie
mg	milligram
min	minute
Ml	milliliter
mm	millimeter
mm Hg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NCE	normochromatic erythrocytes
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
ng	nanogram
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration

PEL	permissible exposure limit
PCE	polychromatic erythrocytes
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard mortality ratio
STEL	short term exposure limit
STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
UMDNJ	University of Medicine and Dentistry New Jersey
U.S.	United States
UF	uncertainty factor
yr	year
WHO	World Health Organization
wk	week

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micrometer
μg	microgram