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

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

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UPDATE STATEMENT

A Toxicological Profile for 1,1,2,2-tetrachloroethane was released in December 1989. 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 relased 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 audience for the toxicological profiles is 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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*Legislative Background

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on 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 PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Green Border Review. Green Border review assures the 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 endpoints.

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.

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PEER REVIEW

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

1. Dr. Martin Alexander, Professor, Soil Microbiology, Dept. of Soil, Crop and Atmospheric Sciences, Cornell University, Ithaca, New York;

2. Mr. Lyman Skory, President, Skory Consulting, Inc.; Health, Environmental and Regulatory Affairs, Midland, Michigan; and

3. Dr. James Withey, Research Scientist, Environmental and Occupational Toxicology Division, Environmental Health Centre, Tunney's Pasture, Ottawa, Ontario, Canada.

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

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

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

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1. PUBLIC HEALTH STATEMENT

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

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal clean-up. 1,1,2,2-Tetrachloroethane has been found in at least 273 of the 1,430 current or former NPL sites. However, it's not known how many NPL sites have been evaluated for this substance. As more sites are evaluated, the sites with 1,1,2,2-tetrachloroethane may increase. This information is important because exposure to this substance may harm your 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. You may be exposed by breathing, eating, or drinking the substance or by skin contact.

If you are exposed to 1,1,2,2-tetrachloroethane, many factors 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, life-style, and state of health.

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

1,1,2,2-Tetrachloroethane is a man-made, colorless, dense liquid that does not burn easily. It is volatile and has a penetrating, sweet odor similar to chloroform. Its production has decreased significantly in the United States. In the past it was used in large amounts to produce other chemicals and as an industrial solvent. 1,1,2,2-Tetrachloroethane was also used to separate other substances, to clean and degrease metals, and in paints and pesticides. Other chemicals are now available to replace this solvent, and large-scale commercial production has

stopped. Its present use appears to be as a chemical intermediate, and information about this use is limited. For more information, see Chapters 3 and 4.

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

Most 1,1,2,2-tetrachloroethane released into the environment eventually moves into the air or ground water. If released on the land, it does not tend to attach to soil particles. When released to surface water, much of the chemical will evaporate back to the air while the remainder may break down due to reactions with water. Similar reactions can take place in soils and sediments. Breakdown of this chemical in both the air and ground water is slow. Half of the chemical is expected to disappear from ground water in 13 months and from air in about 2 months. 1,1,2,2-Tetrachloroethane slowly degrades by losing chlorine atoms. The resulting chemicals are toxic to humans, perhaps even more toxic than the compound itself. It has been estimated that 1,1,2,2-tetrachloroethane should not build up significantly in the bodies of fish or other aquatic organisms. For more information, please see Chapters 4 and 5.

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

Low levels of 1,1,2,2-tetrachloroethane can be present in both indoor and outdoor air. Test studies of city areas show that it is present in only a small number of air samples. Its average concentration in city air could be as high as 57 parts per billion (ppb) (57 parts in 1 ,000,000,000 parts). In rural areas, air concentrations are much lower, typical levels being about 5 parts per trillion (ppt) (5 parts in 1,000,000,000,000 parts) or less. The average concentrations of 1,1,2,2-tetrachloroethane in the indoor air of several homes was 1.8 ppb. Because the air outside these homes did not contain measurable amounts of 1,1,2,2-tetrachloroethane the chemical appears to come from products used within these homes.

1,1,2,2-Tetrachloroethane can also be present in water. A comprehensive survey of representative samples of surface water and ground water, conducted in highly industrialized

areas of New Jersey in 1977-79, found 6% of ground water samples and 11% of surface water samples contaminated with 1,1,2,2-tetrachloroethane. The highest levels found were 2.7 ppb in ground water and 3 ppb in surface water. The New Jersey survey included water supplies used for drinking and water not used for drinking. Although individuals may be exposed to 1,1,2,2-tetrachloroethane from contaminated drinking water, this rarely happens, at least in larger community drinking water systems. A nationwide survey of public drinking water systems that rely on underground sources did not find any supplies containing this pollutant. In a few instances, 1,1,2,2-tetrachloroethane has been found in private well water that may have been used for drinking. 1,1,2,2-Tetrachloroethane has not been reported in food or soil. It is not expected to build up in the food chain.

When a chemical such as 1,1,2,2-tetrachloroethane is used in making other chemicals, it is generally contained in closed automatic systems which are not open to the air. Therefore, workers are not usually exposed to high levels of 1,1,2,2-tetrachloroethane. A national survey conducted in 1981-83 estimated that 4,143 workers were exposed to 1,1,2,2-tetrachloroethane. However, the use of this chemical has decreased since 1983, so the number of exposed workers may now be much lower.

In addition to exposures in air and drinking water, people may be exposed to 1,1,2,2-tetrachloroethane from spills and other accidents or normal operations in workplaces. The compound has been used as a solvent for many operations. If you are exposed to such spills or involved in such work, you are most likely to be exposed by breathing in vapors of the chemical or from skin contact.

1,1,2,2-Tetrachloroethane was found in at least 273 of the 1,430 current or past hazardous waste sites on the National Priorities List (NPL). For more information, see Chapter 5.

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

1,1,2,2-Tetrachloroethane can enter the body when a person breathes air containing the chemical or when the chemical comes into contact with a person's skin. If you accidentally

drank water containing it, 1,1,2,2-tetrachloroethane would be absorbed into your body. 1,1,2,2-Tetrachloroethane is converted to more harmful products in animals and probably in humans. Most of it leaves the body within a few days through the breath or through the urine. For more information, see Chapter 2.

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

1,1,2,2-Tetrachloroethane is not life-threatening unless you intentionally or accidentally drink more than a few spoonfuls at one time or spill a large amount so that you breathe it and get it on your skin. Breathing concentrated fumes of 1,1,2,2-tetrachloroethane (enough so that you notice its sickeningly sweet smell) can rapidly cause fatigue, vomiting, dizziness, and possibly unconsciousness. Most people recover from these effects once they are in fresh air. Breathing, drinking, or having 1,1,2,2-tetrachloroethane come into contact with your skin may cause liver damage, stomachaches, or dizziness if you are exposed long enough to high amounts. The health effects on people from long-term exposure to small amounts of 1,1,2,2-tetrachloroethane are not known.

It is not known whether 1,1,2,2-tetrachloroethane causes cancer in people. In a long-term study, 1,1,2,2-tetrachloroethane caused an increase in liver tumors in mice, but not in rats. The International Agency for Research on Cancer (IARC) has determined that 1,1,2,2-tetrachloroethane cannot be classified as to its ability to cause cancer in humans, while the Environmental Protection Agency (EPA) has determined that the chemical is a possible human carcinogen. Not enough information is available to determine whether exposure to the chemical will cause reproduction problems or birth defects in people. For more information on health effects, see Chapter 2.

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

There are no specific medical tests to determine whether you have been exposed to 1,1,2,2-tetrachloroethane. The symptoms of 1,1,2,2-tetrachloroethane poisoning (stomach-

aches, fatigue, and dizziness) are common to many diseases, and so these symptoms are not very useful in determining whether you were exposed to this particular chemical. 1 ,1,2,2-Tetrachloroethane can affect the liver and medical tests can determine whether the liver is working properly. However, liver disease may have many causes; therefore the presence of liver disease is not a reliable indicator for exposure to 1 ,1,2,2-tetrachloroethane. For more information, see Chapters 2 and 6.

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

The EPA has decided that no more than 0.17 micrograms of 1 ,1,2,2-tetrachloroethane per liter of water (or 0.17 ppb or less than 1 drop in a gallon) should be in lakes and streams. To protect workers during an S-hour shift, the U.S. Occupational Safety and Health Administration (OSHA) has set a limit of 1 parts per million (ppm) (1,000 ppb) of 1,1,2,2-tetrachloroethane in workroom air. The National Institute for Occupational Safety and Health (NIOSH) and the American Conference of Governmental Industrial Hygienists (ACGIH) also recommend that the amount in workroom air be limited to 1 ppm in an 8- to I0-hour work shift.

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, E-29
Atlanta, Georgia 30333
(404) 639-6000

1. PUBLIC HEALTH STATEMENT

This agency can also provide you with information on the location of occupational and environmental health clinics. These clinics specialize in the recognition, evaluation, and treatment of illness resulting from exposure to hazardous substances.

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 of the toxicology of 1,1,2,2-tetrachloroethane. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

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

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 lowestobserved- 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. A-TSDR 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

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

The significance of the exposure levels shown in the 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 (LOAEL) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

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

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

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990a), 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-duration inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute-duration insults, such as

2. HEALTH EFFECTS

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

A few human deaths have been reported following excessive inhalation exposure to 1,1,2,2-tetrachloroethane. Immediately after World War I, gastrointestinal and neurological distress were reported following occupational exposure to a varnish containing 1,1,2,2-tetrachloroethane that was used to cover fabric airplane wings. Although workers generally recovered (see Section 2), at least 4 of 14 workers later became confused, delirious, comatose, and finally died (Willcox et al. 1915). Autopsies revealed extreme liver destruction and fatty degeneration of the liver. The levels of 1,1,2,2-tetrachloroethane in the air were not measured, so inhaled concentrations that may cause death in humans are not known.

Inhalation of 1,1,2,2-tetrachloroethane has also been shown to cause death in animals. Concentrations of 1,1,2,2-tetrachloroethane in air that cause death in rats following 4-6-hour exposures have been consistently reported to be near 1,000 ppm (Carpenter et al. 1949; Deguchi 1972; Schmidt et al. 1980b; Smyth et al. 1969). Deaths in rats occurred at 5,050 ppm after short (30 minutes) exposures (Price et al. 1978). In mice (Horiuchi et al. 1962; Lazarew 1929; Pantelitsch 1933) and guinea pigs (Price et al. 1978), the level that causes death has been reported to be approximately 5,000-6,000 ppm. In animals surviving more than a few days, fatty degeneration of the liver was seen at necropsy (Horiuchi et al. 1962). All exposures from reliable studies that caused death in rats, mice, and guinea pigs are recorded in Table 2-l and plotted in Figure 2-l.

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

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
	ACUTE EXPOSURE						
	Death						
1	Rat (Sprague-Dawley)	30 min				5050 (3/10 died)	Price et al. 1978
2	Rat (Wistar)	4 hr				1253 M (LC_{50})	Schmidt et al. 1980b
3	Mouse (NS)	3 hr				5900 M (3/10 died)	Horiuchi et al. 1962
4	Gn Pig (Hartley)	30 min				6310 (3/10 died)	Price et al. 1978
	Systemic						
5	Rat (Sprague-Dawley)	30 min	Resp	576		5050 (labored respiration)	Price et al. 1978
			Cardio	5050		6310 (cardiac degeneration in 1/10)	
			Hepatic	6310			
			Renal	6310			
			Endocr	6310			
			Ocular	576	5050 (lacrimation)		
			Bd Wt	6310			
6	Mouse (NS)	3 hr	Hepatic		5900M (congestion and fatty degeneration of the liver)		Horiuchi et al. 1962
7	Mouse (Cb)	3 hr	Hepatic		600 F (increased triglycerides and total lipids and decreased ATP contents in liver)		Tomokuni 1969

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

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
8	Mouse (Cb)	3 hr	Hepatic		800 F (increase in liver triglycerides)		Tomokuni 1970
9	Gn Pig (Hartley)	30 min	Resp	576		5050 (labored respiration)	Price et al. 1978
			Cardio	6310			
			Hepatic	6310			
			Renal	6310			
			Endocr	6310			
			Ocular		576 (lacrimation)		
			Bd Wt	6310			
	Neurological						
10	Rat (NS)	6 hr				360 (50% decrease in motor activity)	Horvath and Frantik 1973
11	Rat (Sprague-Dawley)	30 min			576 (reduced activity and alertness)	5050 (narcosis)	Price et al. 1978
12	Gn Pig (Hartley)	30 min			576 (hypoactivity)	5050 (narcosis and tremors)	Price et al. 1978
	INTERMEDIATE EXPOSURE						
	Systemic						
13	Rat (NS)	11 x/29 d 2 d/wk 2 hr/d	Hemato		9000M (decrease in red cell count and hemoglobin content)		Horiuchi et al. 1962
			Hepatic		9000M (congestion and unspecified fatty degeneration of the liver)		
			Bd Wt	9000 M			

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

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference
					Less serious (ppm)	Serious (ppm)	
14	Rat (Sprague-Dawley)	15 wk 5 d/wk 6 hr/d, then 5 hr/d	Resp	130 F			Truffert et al. 1977
			Hemato	130 F			
			Hepatic		130[b] F (increased liver to body weight ratio; signs of hyperplasia, granulation, and cell vacuolization)		
			Renal	130 F			
			Endocr	130 F			
	Neurological						
15	Rat (NS)	11 x/29 d 2 d/wk 2 hr/d				9000 M (hyperactivity, ataxia, followed by unconsciousness)	Horiuchi et al. 1962

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

[b]Used to derive an intermediate inhalation MRL of 0.4 ppm. Concentration converted to an equivalent concentration in humans and divided by an uncertainty factor of 300 (10 for extrapolation from animals to humans, 10 for human variability, and 3 for use of a minimal LOAEL).

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = female; Gn pig = Guinea pig; Hemato = hematological; hr = hour(s); LC_{50} = lethal concentration, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; min = minute(s); NOAEL = no-observable-adverse-effect level; NOS = not otherwise specified; NS = not specified; Resp = respiratory; wk = week(s); wt = weight

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

Acute (≤14 days)

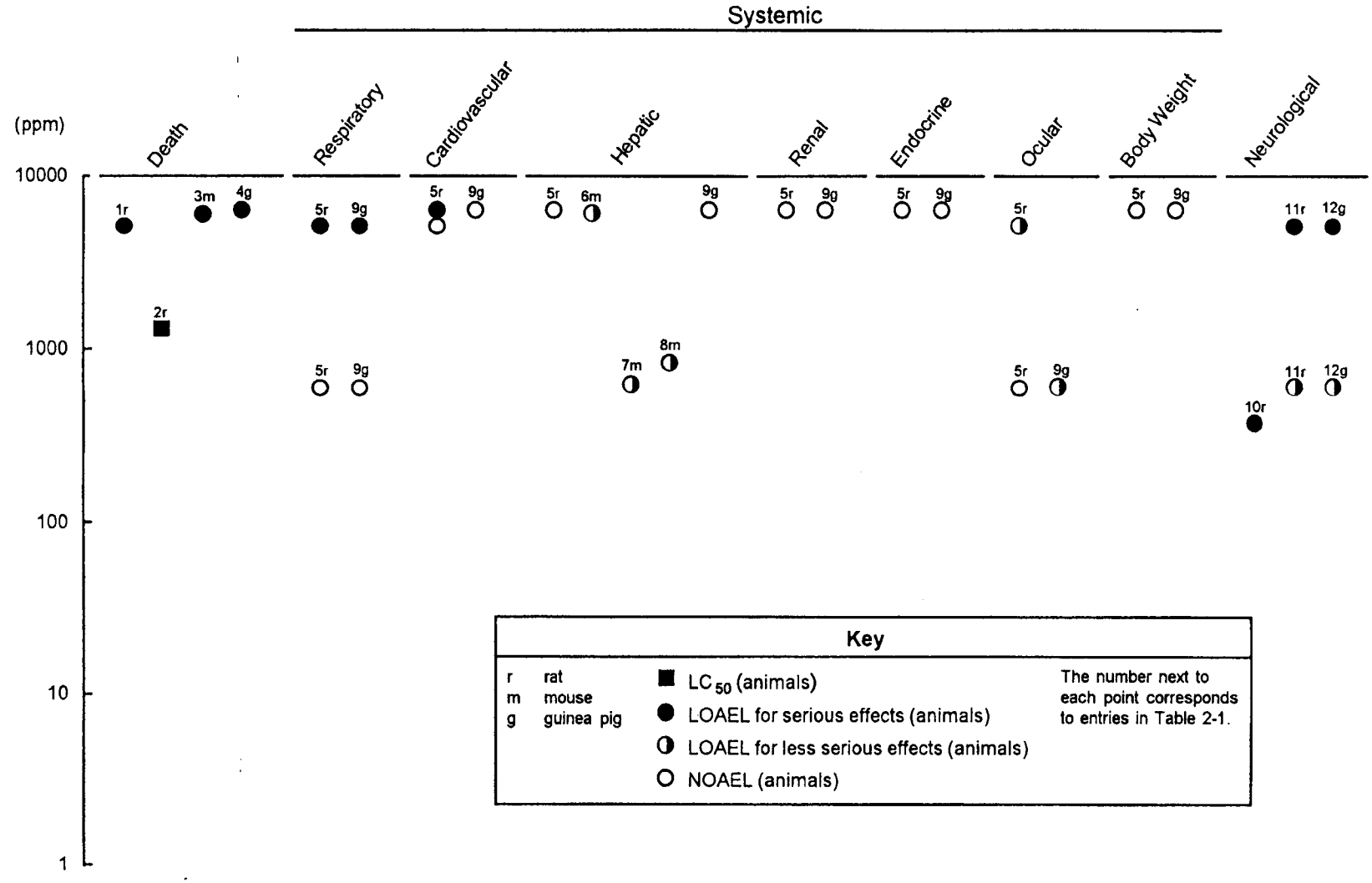
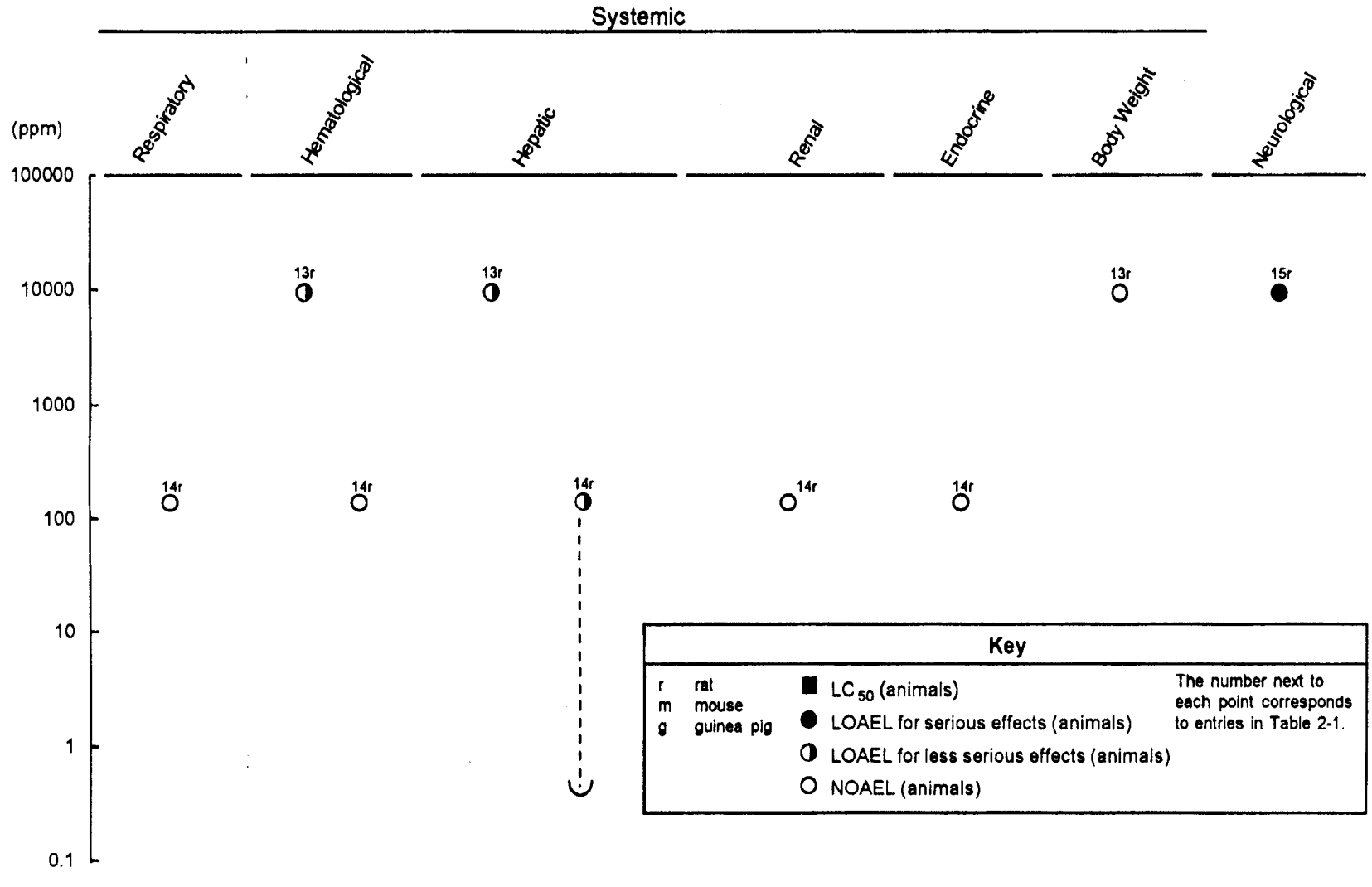


Figure 2-1. Levels of Significant Exposure to 1,1,2,2-Tetrachloroethane - Inhalation

Intermediate (15-364 days)



2. HEALTH EFFECTS

2.2.1.2 Systemic Effects

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

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

Labored respiration was observed in rats and guinea pigs exposed for 30 minutes to 5,050 ppm 1,1,2,2-tetrachloroethane (Price et al. 1978); there was no effect in rats at 576 ppm. Histological examination of the lungs of female rats exposed to 130 ppm intermittently for 15 weeks revealed no treatment-related lesions (Truffert et al. 1977). No histological lesions were found in the lungs of a monkey exposed to 1,974 ppm intermittently for 9 months (Horiuchi et al. 1962). However, only one monkey was studied and a control was not included.

Cardiovascular Effects. Humans exposed to 1,1,2,2-tetrachloroethane in factories showed few, if any, effects on the cardiovascular system. Army workers who were exposed to 1,1,2,2-tetrachloroethane used in a clothing impregnation process showed no increase in deaths due to cardiovascular diseases in a 30-year follow-up period (Norman et al. 1981). Workers exposed to 1,1,2,2-tetrachloroethane in a chemical plant in Italy showed no important clinical changes in cardiovascular function (Gobbato and Bobbio 1968). Exposure levels were not measured in either of these studies.

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

No histopathological changes were seen in the heart of a monkey that was exposed to a time-weighted average (TWA) of 1,974 ppm 1,1,2,2-tetrachloroethane vapors 2 hours per day, 6 days per week for

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9 months (Horiuchi et al. 1962). However, only one monkey was studied, and a control was not included.

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

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

Data regarding gastrointestinal effects in animals following inhalation exposure to 1,1,2,2-tetrachloroethane are limited. One monkey exposed to 1,974 ppm 2 hours per day, 6 days per week for 9 months was reported to experience transient diarrhea and anorexia (Horiuchi et al. 1962). However, no control monkey was included.

Hematological Effects. An increase in the number of large mononuclear cells, white blood cells, and platelets, and slight anemia, were found in workers in an artificial silk factory who were exposed to 1,1,2,2-tetrachloroethane vapors (Minot and Smith 192 1). 1,1,2,2-Tetrachloroethane levels were not accurately measured.

Rats exposed to 130 ppm for 15 weeks showed slightly decreased hematocrit levels, but statistical significance was not reported in this study (Truffert et al. 1977). A monkey exposed to 1,974 ppm intermittently for 9 months showed sporadic changes in hematocrit, red blood cell, and white blood cell counts, but these changes showed no clear trend (Horiuchi et al. 1962). At 9,000 ppm, 2 of 3 male rats showed a decrease in red blood cells and hemoglobin content (Horiuchi et al. 1962).

Hepatic Effects. One of the most significant systemic effects of 1,1,2,2-tetrachloroethane is on the liver. Some humans exposed to 1,1,2,2-tetrachloroethane vapors in the workplace have developed jaundice and an enlarged liver (Coyer 1944; Horiguchi et al. 1964; Jeney et al. 1957; Koelsch 1915;

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Willcox 1915). Specific clinical signs were not associated with specific exposure levels. Vapor concentrations were reported in one study to range from 1.5 to 248 ppm (Jeney et al. 1957).

Liver degeneration, as evidenced by liver congestion and necrosis, was observed in the autopsies of two humans who died after exposure to 1,1,2,2-tetrachloroethane (Willcox et al. 1915). However, one large study showed no significant increases in deaths attributed to liver cirrhosis in over 1,000 men exposed to 1,1,2,2-tetrachloroethane fumes in an Army clothing plant (Norman et al. 1981). Exposure levels were not measured in this study, and the exposure times ranged from about 5 weeks to 1 year.

The liver is also the major target organ for 1,1,2,2-tetrachloroethane toxicity in animals. Mice exposed to 600-800 ppm 1,1,2,2-tetrachloroethane for 3 hours showed fatty changes in the liver (Tomokuni 1969, 1970). Fifty-five female rats exposed to 130 ppm for 5 hours per day, 5 days per week for 15 weeks had increased relative liver weight and signs of hyperplasia (including increased numbers of binuclear cells and appearance of mitoses), granulation, and vacuolization of the liver (Truffert et al. 1977). The LOAEL value of 130 ppm in this study was used to calculate an intermediate-duration inhalation MRL of 0.4 ppm as described in the footnote in Table 2-1 and in Appendix A.

No treatment-related histological effects were found in the liver of rats or guinea pigs exposed to 6,310 ppm for 30 minutes (Price et al. 1978). Hepatic effects described as fine-droplet fatty degeneration, inflammatory changes in the liver, and necrotic foci were described in an acute-duration study in which male rats were exposed to 2 ppm 1,1,2,2,-tetrachloroethane for 4 hours per day, for a total of 8 exposures in 10 days (Gohlke and Schmidt 1972). Schmidt et al. (1980b) also observed fine droplet fatty degeneration in the liver when male rats were exposed to 1,1,2,2-tetrachloroethane vapor for four hours. These studies had a number of limitations that obscured interpretation, including maintaining the rats at elevated room temperatures, a lack of a defined dose-response or durationresponse relationship, and inconsistencies in the reported results.

Rats that were exposed to 9,000 ppm for 2 hours per day, 2 days per week for 4 weeks showed fatty livers (Horiuchi et al. 1962). Mice that were exposed to lethal concentrations (up to 6,600 ppm) of 1,1,2,2-tetrachloroethane for 3 hours showed fatty degeneration of the liver (Horiuchi et al. 1962). Rabbits that were exposed to 15 ppm for 7-11 months showed early signs of liver degeneration at necropsy (Navrotskiy et al. 1971). A monkey exposed to a TWA concentration of 1,974 ppm of

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1,1,2,2-tetrachloroethane for 2 hours per day for 9 months also showed fatty degeneration of the liver (Horiuchi et al. 1962).

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

No treatment-related histological effects were found in the kidneys of rats or guinea pigs exposed to 6,310 ppm for 30 minutes (Price et al. 1978). Similarly, no treatment-related histopathological lesions in the kidney were found in rats exposed to 130 ppm for 15 weeks (Truffert et al. 1977).

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

A number of end points were assessed in two studies of animals exposed to 1 ,1,2,2-tetrachloroethane, but no effects were found at the highest exposure levels (6,310 and 130 ppm) (Price et al. 1978; Trnffert et al. 1977).

Dermal Effects. No studies were located regarding dermal effects in humans or animals following inhalation exposure to 1,1,2,2-tetrachloroethane.

Ocular Effects. Humans exposed to 1,1,2,2-tetrachloroethane vapors (130 ppm) for 10 minutes experienced ocular mucosal irritation (Lehmann and Schmidt-Kehl 1936). Similarly, guinea pigs exposed to 576 ppm for 5 minutes exhibited eye closure and squinting; by 15 minutes lacrimation was common (Price et al. 1978). Rats showed these effects at 5,050 ppm. These ocular effects are due to direct contact of the eyes with the vapors, rather than a true systemic effect due to inhalation of the vapor. These effects are, therefore, presented in Section 2.2.3.2 on ocular effects.

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

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

2.2.1.3 Immunological and Lymphoreticular Effects

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

Rabbits exposed to 1.5 ppm of 1,1,2,2-tetrachloroethane vapor 3 hours per day for 8 months and then immunized with a typhoid vaccine showed a decrease in titers and an increase in the electrophoretic mobility of the specific antibodies when compared to rabbits that were not exposed to 1,1,2,2-tetrachloroethane (Shmuter 1977). No histopathological changes were noted in the spleens of rats which inhaled 100 ppm 1,1,2,2-tetrachloroethane for 6 hours (Deguchi 1972). Since a more complete battery of immune function tests was not performed, this study was not judged to be complete enough to be listed in Table 2-1 or Figure 2-l.

2.2.1.4 Neurological Effects

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

In acute-duration experiments, rats showed a decrease in spontaneous motor activity after –being exposed to 360 ppm for 6 hours (Horvath and Frantik 1973) and mice showed a loss of reflexes after being exposed to 1,091 ppm for 2 hours (Lazarew 1929). As the concentration of, or duration of exposure to, 1,1,2,2-tetrachloroethane increased, mice, rats, and guinea pigs showed some combination of a loss of reflexes, loss of spontaneous motor activity, ataxia, prostration, and narcosis (Lazarew 1929; Pantelitsch 1933; Price et al. 1978). Narcosis was also observed in a cat exposed to 8,300 ppm

for 5 hours (Lehmann 1911). One monkey exposed to a TWA of 1,974 ppm of 1,1,2,2-tetrachloroethane for 2 hours per day for 9 months exhibited unconsciousness after each 2 hour exposure, starting at the fifteenth exposure (Horiuchi et al. 1962). Rats exposed to 9,000 ppm for 2 hours per day, twice a day for 4 weeks exhibited hyperactivity, ataxia, and then unconsciousness (Horiuchi et al. 1962).

The highest NOAEL and all LOAEL values from each reliable study for neurological end points in each species and duration category are recorded in Table 2- 1 and plotted in Figure 2- 1.

2.2.1.5 Reproductive Effects

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

Schmidt et al. (1972) reported atrophy of the seminal vesicles and decreased spermatogenesis after 10 days of exposure to 2 ppm 1,1,2,2-tetrachloroethane. They also found that inhalation of the same level (2 ppm) for 38 weeks had no effect on the ability of male rats to sire healthy fetuses. In rats, no effects on the testes, epididymes, ovaries, or uteruses were seen after inhalation exposure for 30 minutes at 6,310 ppm (Price et al. 1978). In female rats, exposure to 130 ppm of 1,1,2,2-tetrachloroethane vapors for 15 weeks also had no effect on the histology of the reproductive organs (Truffert et al. 1977). Lack of histopathology, however, does not indicate that the female can produce appropriate numbers of healthy offspring. Since no mating studies with females exposed to 1,1,2,2-tetrachloroethane vapors were located in the literature, no values for this effect are indicated on Table 2- 1 or Figure 2- 1.

Inhalation of 1,1,2,2-tetrachloroethane for 9 months to a TWA concentration of 1,974 ppm produced no pathological changes in the testes of 1 monkey (Horiuchi et al. 1962).

2.2.1.6 Developmental Effects

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

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Male rats were exposed to 2 ppm 1,1,2,2-tetrachloroethane 4 hours per day, for an unspecified number of times during a 9-month period. One week before the end of the exposure period, exposed males and control males were mated with unexposed females and the F1 generation was observed for 12 weeks. There was no effect on the number of offspring per litter, neonatal body weight, viability of the offspring, sex ratios, and body weight on day 84. No gross malformations were observed in the offspring (Schmidt et al. 1972).

2.2.1.7 Genotoxic Effects

No studies were located regarding the genotoxic effects in humans or animals following inhalation exposure to 1,1,2,2-tetrachloroethane. Other genotoxicity studies are discussed in Section 2.5.

2.2.1.8 Cancer

A group of 1,099 army workers who were exposed to 1,1,2,2-tetrachloroethane vapors in a clothing processing plant showed a very slight increase in the incidence of death due to genital cancers, leukemia, and lymphomas when compared to similar workers whose duties did not involve exposure to 1,1,2,2-tetrachloroethane (Norman et al. 1981). The individuals could have been exposed dermally or by inhalation, but specific exposure levels were not measured. Since the increased incidence was small, no significant excesses were found, and other confounding factors may have been present (i.e., exposure to other chemicals and a lack of occupational histories following exposure), the authors I concluded that the results are difficult to interpret and the observed incidences of cancer may not have been due to 1,1,2,2-tetrachloroethane exposure. This information is inconclusive as to whether 1 ,1,2,2-tetrachloroethane causes cancer in humans.

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

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2.2.2 Oral Exposure

2.2.2.1 Death

A number of human suicides from drinking 1,1,2,2-tetrachloroethane have been reported. The amount consumed varied among individuals, making a minimum lethal dose difficult to determine. Based on the amount found in the stomach, the approximate minimum amounts consumed in these cases were estimated to be 4,100 mg/kg (Hepple 1927), 357 mg/kg (Lilliman 1949), 1,100-9,600 mg/kg (Mant 1953) and an unknown quantity (Elliot 1933; Forbes 1943). The subjects who were poisoned usually lost consciousness within about an hour and died 3-20 hours post ingestion, depending on the amount of food in the stomach. Postmortem examination showed congestion in the lungs in some cases.

The levels that caused death in rats have all been within a narrow range: 319 mg/kg (Smyth et al. 1969), 250 mg/kg (Gohlke et al. 1977), 300 mg/kg/day for 3-4 days (Dow 1988), and 330 mg/kg (Schmidt et al. 1980a). The most complete study (Gohlke et al. 1977) administered the substance by gavage in peanut oil. In a chronic-duration mouse study, a level of 284 mg/kg/day caused death in a majority of exposed mice, after 70 weeks of exposure (NCI 1978).

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

2.2.2.2 Systemic Effects

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

Respiratory Effects. Autopsy reports in humans following suicidal ingestion of at least 1,100 mg/kg of 1,1,2,2-tetrachloroethane revealed congestion and edema in the lungs (Hepple 1927; Mant 1953), but this did not appear to be the primary cause of death. A case of exposure at 9,600 mg/kg was reported to have caused lung collapse (Mant 1953). African men and women

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL			Reference
					Less Serious (mg/kg/day)		Serious (mg/kg/day)	
	ACUTE EXPOSURE							
	Death							
1	Human	once (IN)					4100 M (death)	Hepple 1927
2	Human	once (IN)					357 (death)	Lilliman 1949
3	Human	once (IN)					9600 M (death)	Mant 1953
4	Human	once (IN)					1100 M (death)	Mant 1953
5	Rat (NS)	once (GO)					250 M (LD_{50})	Gohlke et al. 1977
6	Rat (Wistar-C)	once (GO)					330 M (LD_{50})	Schmidt et al. 1980a
7	Rat (Carnworth -Wistar)	once (G)					319 M (LD_{50})	Smyth et al. 1969
	Systemic							
8	Human	once (IN)	Gastro		357	(congestion of stomach lining)		Lilliman 1949
			Hepatic		357	(slight liver congestion)		

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
9	Human	once (IN)	Resp			9600 M (lung collapse)	Mant 1953
			Gastro		9600M (congestion of esophagus and stomach)		
10	Human	once (IN)	Resp			1100 M (extreme lung congestion and edema)	Mant 1953
			Cardio			1100 M (epicardial and endocardial anoxic petechial hemorrhage)	
			Gastro		1100M (pronounced congestion of gastric mucosa)		
			Hepatic	1100M			
			Renal	1100M			
11	Human	once (IN)	Resp			96 (shallow and rapid respiration)	Sherman 1953
			Cardio			96 (faint pulse)	
12	Human	once (IN)	Resp			100 (shallow breathing)	Ward 1955
			Cardio			100 M (low blood pressure, 60/46)	
13	Rat (Osborne-Mendel)	3-4 d 1x/d (GO)	Hepatic	25M	75M (hyperplasia)		Dow 1988
			Bd Wt	150M	300M (16% depression in final body weight relative to controls)		
14	Rat (Wistar-C)	once (GO)	Hepatic		100M (necrosis and fatty degeneration)		Schmidt et al. 1980a

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
15	Mouse (B6C3F1)	4 d 1x/d (GO)	Hepatic	25M	75M (centrilobular swelling)		Dow 1988
			Bd Wt	300M			
	Neurological						
16	Human	once (IN)				96 (reversible coma)	Sherman 1953
17	Human	once (IN)				100 (reversible narcosis and absence of corneal and pupillary reflexes)	Ward 1955
18	Rat (Osborne-Mendel)	3-4 d 1x/d (GO)		150M		300 M (CNS depression)	Dow 1988
19	Rat (Wistar)	once (G)		25 F		50 F (blocked avoidance learning)	Wolff 1978
	INTERMEDIATE EXPOSURE						
	Systemic						
20	Rat (Osborne-Mendel)	6 wk 5 d/wk (GO)	Bd Wt	100M		178 M (38% reduction in body weight gain)	NCI 1978
				56[b] F		100 F (24% reduction in body weight gain)	

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
21	Mouse (B6C3F1)	6 wk 5 d/wk (GO)	Bd Wt	316			NCI 1978
	CHRONIC EXPOSURE						
	Death						
22	Mouse (B6C3F1)	78 wk 5 d/wk (GO)				284 M (33/50 died in week 69-70)	NCI 1978

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
	Systemic						
23	Rat (Osborne-Mendel)	78 wk 5 d/wk (GO)	Resp		43[c] F (labored respiration, wheezing, nasal discharge) 62 M		NCI 1978
			Cardio	108 M 76 F			
			Gastro	108 M 76 F			
			Hepatic	108 M 76 F			
			Renal	108 M 76 F			
			Endocr	108 M 76 F			
			Dermal	108 M 76 F			
			Ocular		62 M (squinted or reddened eyes with reddish brown discharge) 43 F		
			Bd Wt	76 F 62 M		108 M (20% decrease in body weight gain)	

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
24	Mouse (B6C3F1)	78 wk 5 d/wk (GO)	Resp	284			NCI 1978
			Cardio	284			
			Gastro	284			
			Hepatic	284			
			Renal	142		284 (tubular nephrosis in males, hydronephrosis in females)	
			Endocr	284			
			Dermal	284			
			Bd Wt	284			
	Reproductive						
25	Rat (Osborne-Mendel)	78 wk 5 d/wk (GO)		108 M 76 F			NCI 1978
26	Mouse (B6C3F1)	78 wk 5 d/wk (GO)		284			NCI 1978

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

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

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

[b]Used to derive an intermediate oral MRL of 0.6 mg/kg/day; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[c]Used to derive a chronic oral MRL of 0.04 mg/kg/day; dose divided by an uncertainty factor of 1000 (10 for extrapolation from animals to humans, 10 for human variability, and 10 for use of a LOAEL).

Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; CNS = central nervous system; d = day(s); Endocr = endocrine; F = female; (G) = gavage; Gastro = gastrointestinal; (GO) = gavage in oil; (IN) = ingestion; LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; NOAEL = no-observable-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s); x = times

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

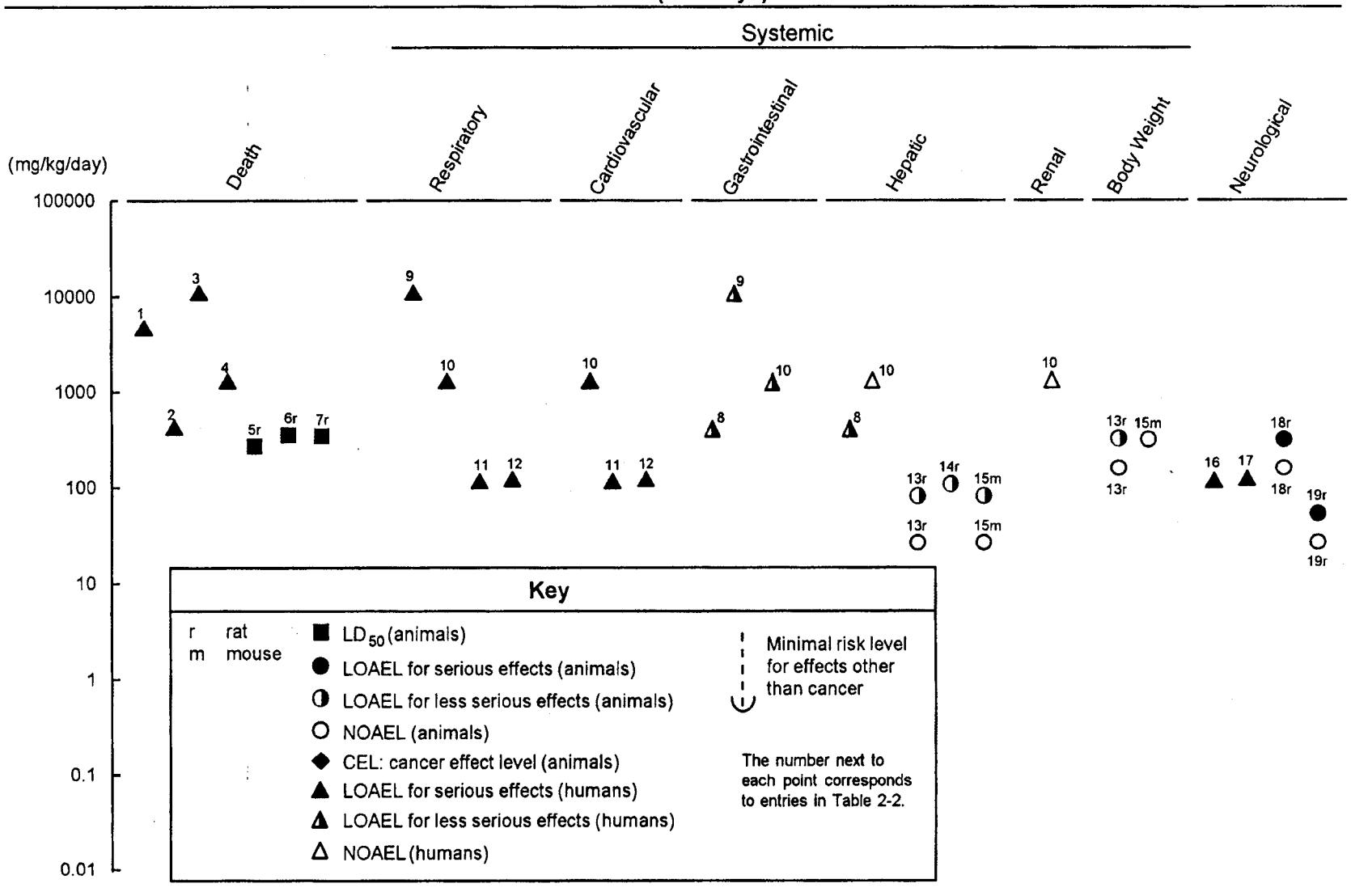


Figure 2-2. Levels of Significant Exposure to 1,1,2,2-Tetrachloroethane - Oral

Intermediate (15-364 days)

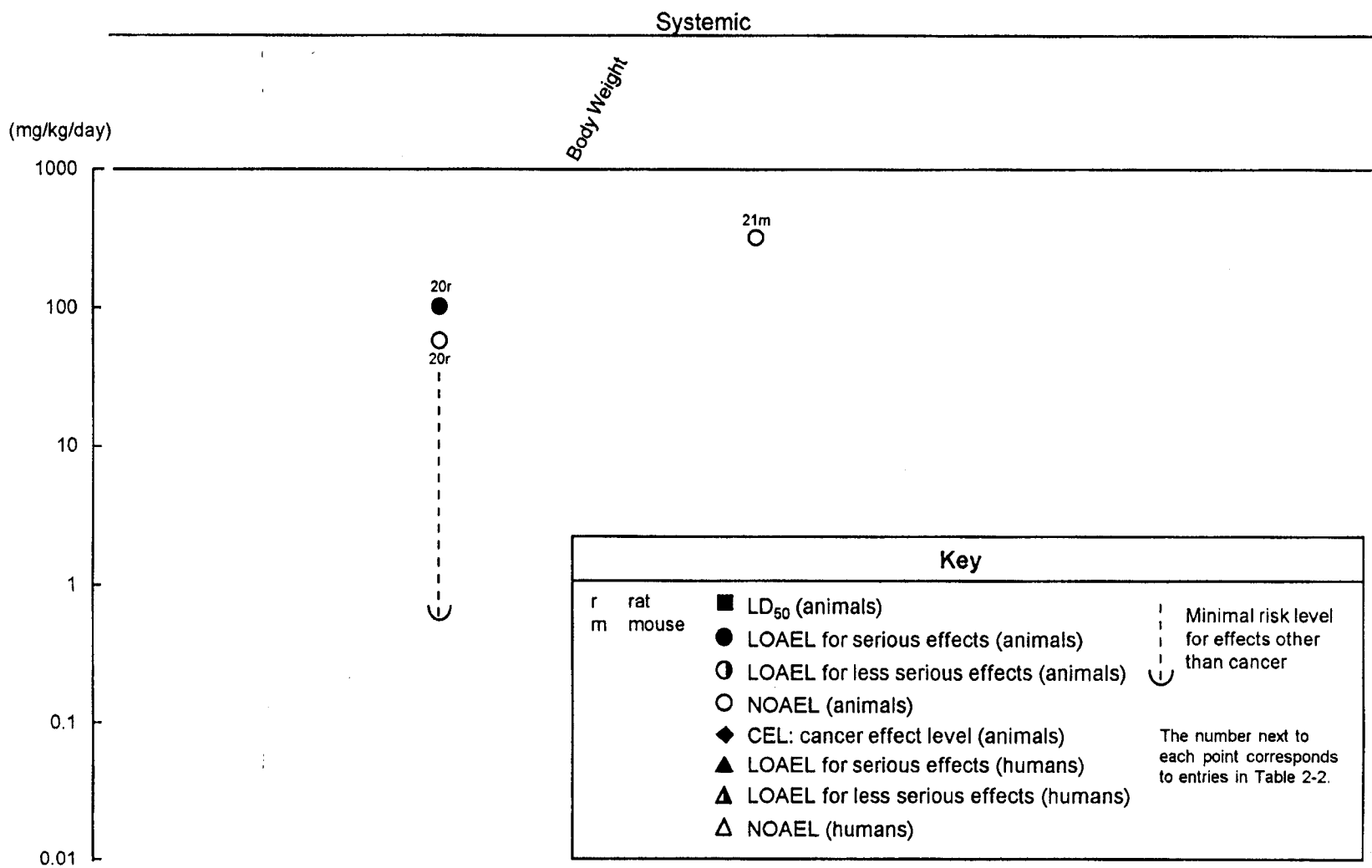
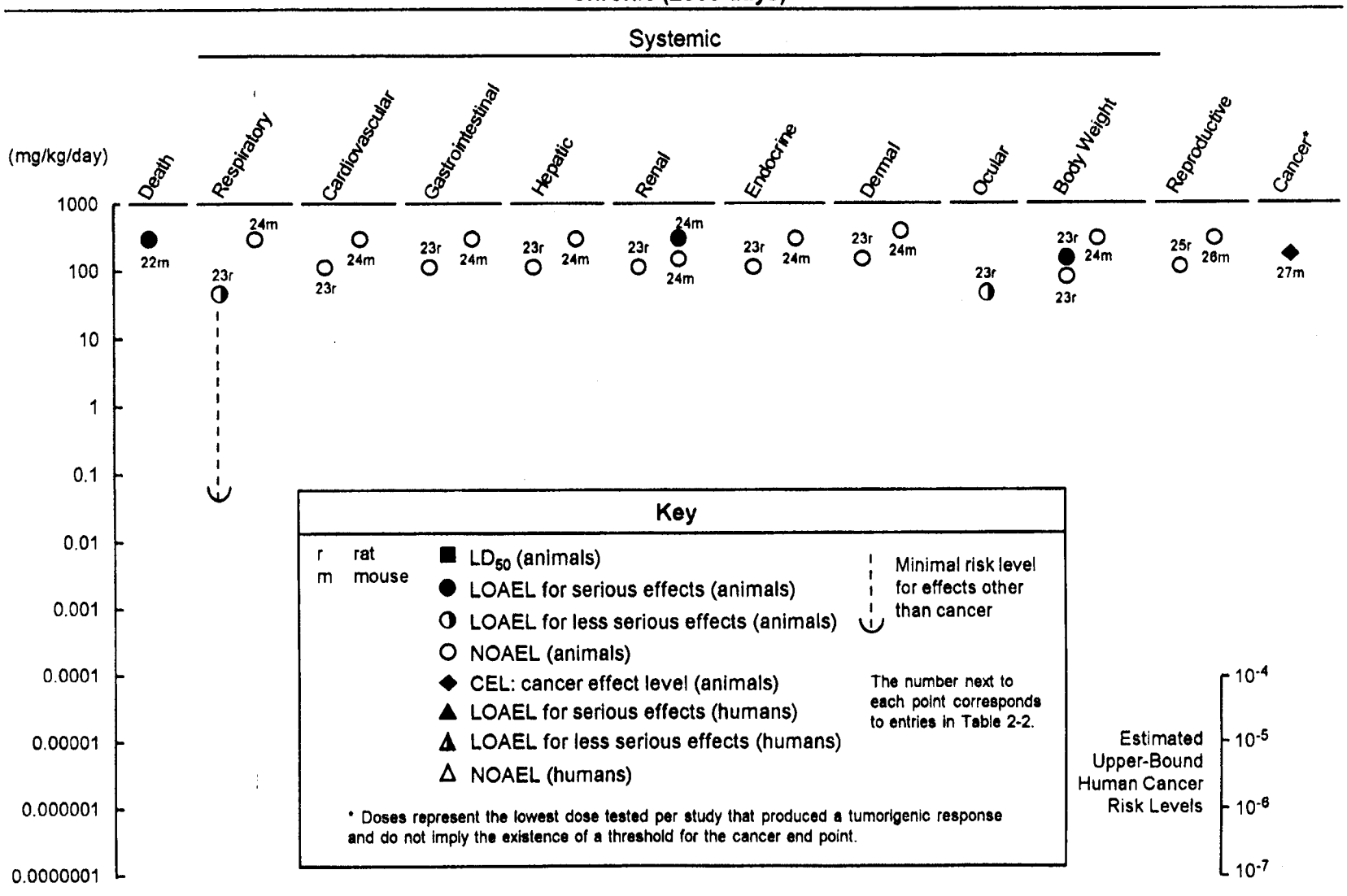


Figure 2-2. Levels of Significant Exposure to 1,1,2,2-Tetrachloroethane - Oral (cont.)



2. HEALTH EFFECTS

accidentally given oral doses of undiluted 1,1,2,2-tetrachloroethane (approximately 70-117 mg/kg) experienced shallow breathing during ensuing unconsciousness (Sherman 19.53; Ward 1955).

Rats that received up to 8 mg/kg/day of 1,1,2,2-tetrachloroethane for up to 17 weeks showed no histopathology of the trachea (Gohlke et al. 1977); the lungs were not examined. Longer-term exposure in rats at higher levels (up to 108 mg/kg/day for 78 weeks) produced labored respiration, wheezing, and/or nasal discharge in all groups during the first year and increased as the animals aged. Based on a LOAEL of 43 mg/kg/day for respiratory effects in female rats, a chronic oral MRL was derived as described in the footnote in Table 2-2 and in Appendix A. Mice treated for the same duration at 284 mg/kg/day experienced no respiratory effects (NCI 1978).

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

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

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

Hepatic Effects. Autopsy reports showed no evidence of damage to the livers of humans who ingested suicidal doses of 1,1,2,2-tetrachloroethane (Mant 1953). The lack of effect in the liver can be ascribed to the rapid lethality. In another autopsy report, slight congestion of the liver was reported from an accidental poisoning or suicide attempt with 1,1,2,2-tetrachloroethane (Lilliman -1.949).

Rats that received a single oral dose of 100 mg/kg of 1,1,2,2-tetrachloroethane showed unspecified necrosis and fatty degeneration, increased serum leucine aminopeptidase, increased liver ascorbic acid, and increased liver triglyceride levels, but no changes in relative liver weight or body weight (Schmidt et al. 1980a). Centrilobular swelling was observed in mice after a dose of 75 mg/kg/day of

2. HEALTH EFFECTS

1,1,2,2-tetrachloroethane for 4 days (Dow 1988); there were no effects in the livers of rats or mice at a dose of 25 mg/kg/day. At a dose of 300 mg/kg there were increases in mitosis in the mouse hepatocytes. Rats that were gavaged with doses of 3.2 or 8 mg/kg/day of 1,1,2,2-tetrachloroethane for longer periods of time (2 days to 17 weeks) showed minor histological changes in the liver, including inflammation, necrosis, and fatty degeneration (Gohlke et al. 1977).

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

Rats treated with 3.2 mg/kg/day of 1,1,2,2-tetrachloroethane for up to 16 weeks showed isolated necrosis of the tubular cortex in the kidney (Gohlke et al. 1977). However, in studies conducted by the NCI (1978), rats treated with up to 108 mg/kg/day for 78 weeks showed no gross or histopathological changes in the kidney. Mice treated for the same duration at 142 mg/kg/day also showed no changes, but at 284 mg/kg/day, male mice died of tubular nephrosis and females experienced hydronephrosis.

Endocrine Effects. No studies were located regarding endocrine effects in humans after oral exposure to 1,1,2,2-tetrachloroethane. Rat adrenal and thyroid glands showed changes due to exposure for 120 days to 1,1,2,2-tetrachloroethane. In the thyroid, cell sizes were changed and follicular desquamation was found, and the adrenals showed changes in lipoid content (Gohlke et al. 1977).

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

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

2. HEALTH EFFECTS

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

In rats treated with 300 mglkglday by gavage for 3-4 days, body weights were depressed by 16% (Dow 1988). No depression in body weight was observed at 150 mg/kg/day. In the 6-week range finding study by NCI (1978), male rats given 178 mg/kg/day by gavage had a 38% reduction in body weight gain, while female rats given 100 mg/kg/day had a 24% reduction. Based on a NOAEL of 56 mg/kg/day for no decreased body weight gain in female rats, an intermediate-duration oral MRL of 0.6 mg/kg/day was derived for 1,1,2,2-tetrachloroethane, as described in the footnote in Table 2-2 and in Appendix A. In contrast, no effects on body weight gain were seen in mice similarly exposed at doses 1316 mg/kg/day. Body weight gain was also depressed in rats, but not mice, treated by gavage with 1,1,2,2-tetrachloroethane for 78 weeks (NCI 1978). Weights of female rats treated with 76 mg/kg/day appeared lower than control weights throughout the treatment; however, by the end of the observation period, no difference was observed compared with the controls. Male rats treated with 108 mg/kg/day, but not 62 mg/kg/day, were 20% lighter than vehicle controls at week 75.

2.2.2.3 Immunological and Lymphoreticular Effects

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

The available animal data on these effects showed that oral administration of 8 mg/kg/day of 1,1,2,2-tetrachloroethane to rats for 16 weeks caused no histopathological changes in the spleen (Gohlke et al. 1977). In the NCI (1978) study, no gross or histological alterations were seen in the spleen or lymph nodes of rats and mice exposed to 1,1,2,2-tetrachloroethane at doses up to 284 mg/kg/day for 78 weeks. Since the histology of the spleen alone is not a good indicator of immune function, and since more specific tests of immune function were not performed;-these doses cannot be considered NOAELs for immunological effects.

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2.2.2.4 Neurological Effects

By mistake, 3 mL (about 70-l 17 mg/kg) of 1,1,2,2-tetrachloroethane was given orally to several African men and women as a treatment for parasites (Sherman 1953; Ward 1955). The patients lost consciousness within an hour, but were subsequently revived with no apparent after effects. The patients understandably refused further treatment or observation at these clinics.

Rats receiving doses of 300 mg/kg/day for 3-4 day experienced significant central nervous system depression and debilitation (Dow 1988). No more elaborate description of these effects were provided, however. Rats receiving a single 50 mg/kg dose displayed significantly decreased avoidance learning. This effect was not detected at 25 mg/kg (Wolff 1978).

The LOAEL values for each reliable study for neurological effects after acute-duration exposure are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.5 Reproductive Effects.

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

Reproductive effects were found in rats dosed at 3.2 mg/kg/day, 82 times in 120 days (Gohlke et al. 1977). A high incidence of interstitial edema in the testes, clumped sperm, and epithelial cells in the tubular lumen were observed. Partial necrosis and totally atrophied tubules, giant cells, and two-row germinal epithelial cells with disturbed spermatogenesis were also observed. Some of these changes (unspecified) persisted during the 2-week follow-up observation period. No other reproductive indices were examined. This study had a number of limitations, including an unusual experimental design in which the rats were exposed at a high temperature (35 "C), and uncertainties regarding the language translation. Longer term exposures at higher dose levels, however, produced no gross or- histological alterations in the reproductive organs of male or female rats or mice (NCI 1978). In these studies, male rats were dosed at a level of 108 mg/kg/day for 78 weeks, female rats were dosed at 76 mglkglday for the same period, and mice were dosed at 284 mg/kg/day for the same period. No apparent reason for these discrepancies in effects reported at widely varying doses were found, but the

limitations of the former study complicate its evaluation and make comparison with other studies difficult.

The highest NOAEL and all LOAEL values from all reliable studies 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

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

2.2.2.7 Genotoxic Effects

No studies were located regarding the genotoxic effects in humans or animals following oral administration of 1,1,2,2-tetrachloroethane. Other genotoxicity studies are discussed in Section 2.5.

2.2.2.8 Cancer

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

The initiating and promoting effects of a dose of 99 mg/kg doses to rats was investigated by Story et al. (1986). The study found no initiating action of 1,1,2,2-tetrachloroethane, but a significant promotional effect as indicated by increases in the activity of gamma-glutamyl transpeptidase was reported.

A highly significant dose-related trend in the incidence of hepatocellular carcinomas in both male and female mice has-been reported following oral administration of 142 and 284 mg/kg/day of 1,1,2,2-tetrachloroethane for 78 weeks. The increased incidences were statistically significant at both dose levels compared with controls. No statistically significant increase in the incidence of tumors was found in the treated rats when compared to the controls (NCI 1978). However, rats have been shown to have a low incidence of tumors when treated with carbon tetrachloride, when used as a positive control. This indicated to the NCI that rats may not be sensitive enough to detect tumors

caused by 1,1,2,2-tetrachloroethane. The NCI (1978) concluded that the results in rats provided no evidence of a carcinogenic response in the strain of rats used in this study.

The EPA (IRIS 1994) has calculated an oral slope factor of 0.2 $(mg/kg/day)^{-1}$ for 1,1,2,2-tetrachloroethane, based on the NCI (1978) study showing increased hepatocellular carcinomas in female mice. This ql* corresponds to upper bound individual lifetime cancer risks ranging from $5x10^{-4}$mg/kg/day (10^{-4} risk level) to $5x10^{-7}$ mg/kg/day (10^{-7} risk level). These risk levels are indicated on Figure 2-2.

2.2.3 Dermal Exposure

2.2.3.1 Death

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

The dermal LD_{50} (lethal dose, 50% kill) for 1,1,2,2-tetrachloroethane in rabbits is 6,360 mg/kg (Smyth et al. 1969) and is recorded in Table 2-3.

2.2.3.2 Systemic Effects

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

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, and renal effects in animals after dermal exposure to 1,1,2,2-tetrachloroethane. The LOAEL values for each reliable study for systemic effects in each species and duration category are recorded in Table 2-3.

Dermal Effects. Direct application of 514 mg/cm^2 of 1,1,2,2-tetrachloroethane for 16 hours damaged the skin of guinea pigs, causing karyopyknosis and pseudoeosinophilic infiltration (Kronevi et al. 1981). Application of 1,1,2,2-tetrachloroethane (concentration not reported) to the shaved abdomen of rabbits caused hyperemia, edema, and severe blistering (Dow 1944).

Ocular Effects. Humans exposed to 1,1,2,2-tetrachloroethane vapors (130 ppm) for 10 minutes experienced mucosal irritation around the eyes (Lehmann and Schmidt-Kehl 1936). Similarly, guinea pigs exposed to 576 ppm for 5 minutes demonstrated eye closure and squinting; by 15 minutes lacrimation was common (Price et al. 1978). Rats showed these effects at 5,050 ppm. These ocular effects are due to direct contact of the eyes with the vapors rather than a true systemic effect due to inhalation of the vapor. These effects are also described in Section 2.2.1.2 on inhalation effects.

2.2.3.3 Immunological and Lymphoreticular Effects

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

No studies were located regarding immunological or lymphoreticular effects in animals after dermal exposure to 1,1,2,2-tetrachloroethane.

2.2.3.4 Neurological Effects

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

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

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

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL		Reference Chemical Form
				Less Serious	Serious	
ACUTE EXPOSURE						
Systemic						
Rat (Sprague-Dawley)	30 min	Ocular	576 ppm	5050 ppm	(lachrimation)	Price et al. 1978
Gn Pig NS	once	Dermal		514 mg/cm^2	(moderate karyopyknosis and cellular infiltration)	Kronevi et al. 1981

Gn pig = Guinea pig; LOAEL = lowest-observable-adverse-effect level; min = minute(s); NOAEL = no-observable-adverse-effect level; NS = not specified

2. HEALTH EFFECTS

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

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

2.3 TOXICOKINETICS

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

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

A study in human volunteers was carried out in which a bulb containing ^{38}Cl-labelled 1,1,2,2-tetrachloroethane was inserted into their mouths; they immediately inhaled deeply, held their breaths for 20 seconds, and then exhaled through a trap containing granulated charcoal. The excretion of the absorbed compound in the breath and the partition coefficients between blood and air were measured.

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The study showed that 97% of a single breath of 1,1,2,2-tetrachloroethane is absorbed systemically (Morgan et al. 1970). Two humans were reported to retain approximately 50% of inspired 1,1,2,2-tetrachloroethane, but details on exposure duration and dose were not specified (Lehmann and Schmidt-Kehl 1936).

The total body burden of 1,1,2,2-tetrachloroethane in rats and mice exposed to a vapor concentration 10 ppm for 6 hours was 36 micromole equivalents per kg in rats and 128 micromole equivalents per kg in mice (Dow 1988).

2.3.1.2 Oral Exposure

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

The total body burden of 1,1,2,2-tetrachloroethane in rats and mice administered 150 mg/kg oral doses of the chemical by gavage in corn oil was about 900 micromole equivalents per kg for both species (approximately 150 mg/kg), indicating that the compound is very well absorbed orally (Dow 1988).

Rats and mice that received 1,1,2,2-tetrachloroethane orally absorbed most of the dose (Milman et al. 1984), but no further details were available on this study. Another study showed that rats and mice given 1,1,2,2-tetrachloroethane via the oral route metabolized approximately 70% of the dose within 48 hours, indicating that at least this much was absorbed (Mitoma et al. 1985).

2.3.1.3 Dermal Exposure

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

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

2. HEALTH EFFECTS

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

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

2.3.2.2 Oral Exposure

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

A high level of hepatic protein-binding radioactivity was seen in mice administered 1,1,2,2-tetrachloroethane by gavage, followed by a single dose of ^{14}C-1,1,2,2-tetrachloroethane. The amount of 1,1,2,2,-tetrachloroethane-derived radioactivity bound to liver protein was about 2 times that seen in rats (Mitoma et al. 1985). The difference in toxicity of 1,1,2,2-tetrachloroethane in rats and mice may well be due to the higher metabolic rate in mice.

2.3.2.3 Dermal Exposure

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

2.3.3 Metabolism

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

In rats and mice, 60-80% of the administered dose is metabolized and excreted within 48-72 hours following oral doses ranging from 25 to 200 mg/kg (Dow 1988; Mitoma et al. 1985) or an intraperitoneal dose ranging from 210 to 320 mg/kg (Yllner 1971).

1 ,1,2,2-tetrachloroethane is metabolized to trichloroethanol, trichloroacetic acid, and dichloroacetic acid (Ikeda and Ohtsuji 1972; Mitoma et al. 1985). Dichloroacetic acid is then broken down to glyoxylic

acid and formic acid (Yllner 1971). These metabolic pathways are shown in Figure 2-3. Nonenzymatic degradation of 1,1,2,2-tetrachloroethane was thought to occur via dehydrochlorination to form trichloroethylene and tetrachloroethylene in mice (Yllner 1971). More recent data from an in vitro study using rat livers (Koizumi et al. 1982) suggest that the formation of trichloroethylene and tetrachloroethylene from 1,1,2,2-tetrachloroethane may be both enzymatic and non-enzymatic. The above studies relied on calorimetric tests for determination of metabolic products. More definitive studies using gas chromatography and mass spectrometry demonstrated that the hepatic microsomal cytochrome P-450 system in rats catalyzes the conversion of 1,1,2,2-tetrachloroethane to dichloroacetic acid in vitro (Casciola and Ivanetich 1984; Halpert 1982). Those authors indicated that the hydroxylation of 1,1,2,2-tetrachloroethane to form the reactive dichloroacetic acid is the predominant initial metabolic pathway that initiates a series of reactions that leads to the formation of glyoxylic and formic acid.

Eriksson and Brittebo (1991) demonstrated that 1,1,2,2-tetrachloroethane is metabolized in mice by cytochrome P-450 to products that bind to the epithelium of the respiratory and upper alimentary tracts following intravenous administration (3 mg/kg) to mice. The metabolism of 1,1,2,2-tetrachloroethane was increased by chronic ethanol consumption (Sato et al. 1980) and by fasting (Nakajima and Sato 1979) in rats. These treatments did not increase total microsomal cytochrome P-450 content, but are indicative of the involvement of cytochrome P-450 isoenzyme 2El.

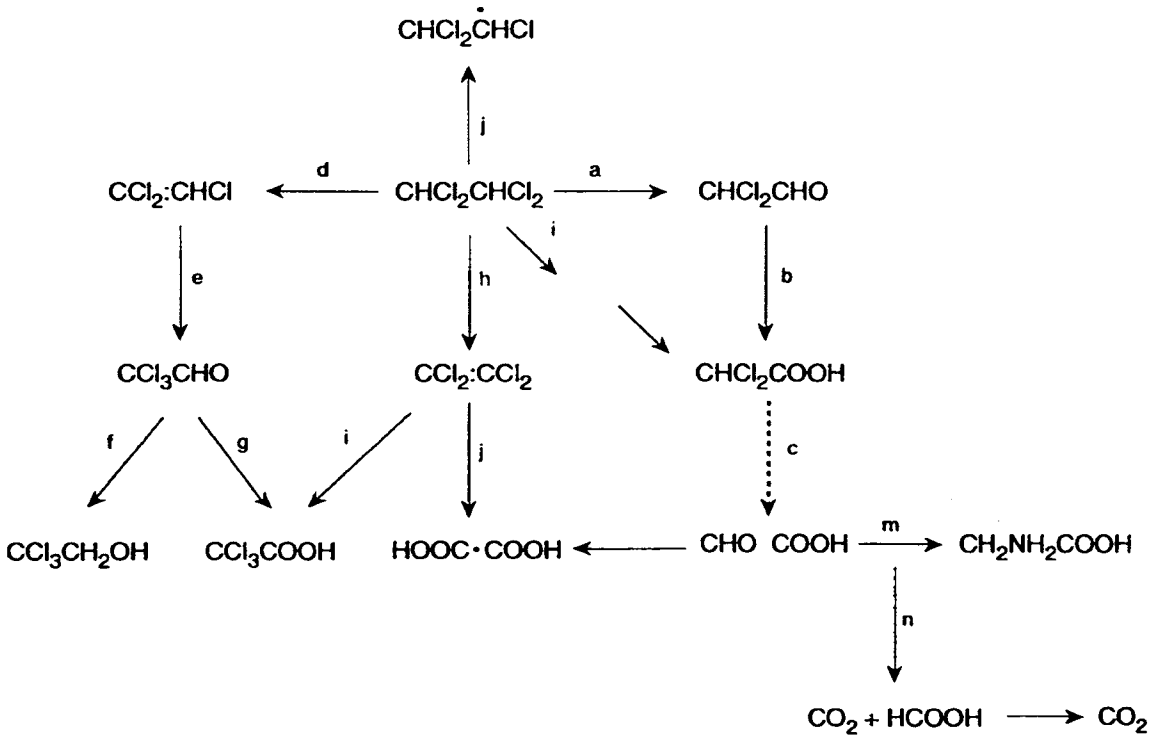
2.3.4 Excretion

2.3.4.1 Inhalation Exposure

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

The excretion of-1,1,2,2-tetrachloroethane was tracked for 72 hours following exposure of rats and mice to vapor concentrations of 10 ppm ^{14}C-l,1,2,2-tetrachloroethane for 6 hours (Dow 1988). More than 90% of the absorbed dose was metabolized in both species. The percentage of the recovered radioactivity was reported as follows: in rats, 33% in breath, 19% in urine, and 5% in feces; in mice, 34% in breath, 26% in urine, and 6% in feces.

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



Note: 1,1,2,2-Tetrachloroethane is mainly metabolized (a) by a stagewise hydrolytic cleavage of carbon-chlorine bonds via dichloroacetic acid (b) to glyoxylic acid (c), which is further metabolized (l,m,n). An alternative route (d) is non-enzymic dehydrochlorination to trichloroethylene, which is further metabolized (e,f,g) to trichloroacetic acid + trichloroethanol. Route (h) is oxidation to tetrachloroethylene. Route (i) is the P-450-dependent oxidation, followed by dehydrohalogenation, to form dichloroacetyl chloride. Route (j) is reductive dechlorination.

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

2.3.4.2 Oral Exposure

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

The excretion of 1,1,2,2-tetrachloroethane was followed for 72 hours following oral administration of 1.50 mg/kg doses to rats and mice (Dow 1988). Greater than 90% of the absorbed dose was metabolized in both species. In rats, 41% was excreted in breath, 23% in urine, and 4% in feces. In mice, 51% was excreted in breath, 22% in urine, and 6% in feces.

Mice given an oral dose of 1,1,2,2-tetrachloroethane excreted about 10% of the dose unchanged in the breath. The rest was metabolized and excreted in the breath as CO_2 (10%), in the urine and feces (30%, measured together), and retained in the carcass (27%) after 48 hours. Rats showed similar patterns of excretion (Mitoma et al. 1985). The most comprehensive study of the metabolism and excretion of 1,1,2,2-tetrachloroethane was an intraperitoneal study in mice using ^{14}C-labeled 1,1,2,2-tetrachloroethane. This study showed that after 72 hours, about 4% of the radioactivity was expired unchanged in the breath, 50% was expired as CO_2 ,28% was excreted in the urine, 1% was in the feces, and 16% remained in the carcass (Yllner 1971).

2.3.4.3 Dermal Exposure

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

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

2.4 MECHANISMS OF ACTION

As 1,1,2,2-tetrachloroethane is a volatile, lipophilic molecule of small molecular size, it is well absorbed from both respiratory and gastrointestinal tracts and rapidly distributes throughout tissue compartments by typical passive diffusion processes.

Chlorinated hydrocarbons share similar metabolic fates that involve both oxidative and reductive reactions. These reactions are intimately related to the mechanisms by which halocarbons are activated to proximate toxins. The following mechanisms of activation and toxicity have been investigated for 1,1,2,2-tetrachloroethane.

Toxification Mediated through Oxidation. The presence of the functional group consisting of a terminal dichloromethyl moiety in a molecule, as typified by the drug chloramphenicol, is known to confer toxicity. Chloramphenicol and other dichloromethyl compounds are hydroxylated to form, after spontaneous dehydrohalogenation, reactive acyl chloride intermediates (Halpert 198 1; Halpert et al. 1986) which subsequently bind to crucial proteins to exert their effects. Alternately, these acid chlorides can hydrolyze to form their respective acids. There was clear evidence in the literature reviewed that these pathways were operant for 1 ,I ,2,2-tetrachloroethane. Cytochrome P-450 was found to catalyze the formation of both dichloroacetylated protein adducts (Halpert 1982) and dichloroacetic acid (Halpert 1981). As discussed in Section 2.3.3, these biotransformation reactions were increased by chronic ethanol consumption and fasting, preconditions that are known to induce the levels of cytochrome P-450 isoenzyme IIEl (Johansson et al. 1988; Soucek and Gut 1992). Significantly, a number of low molecular weight volatile halocarbons are metabolized by this isoform, suggesting that it-may be the major contributor to the metabolism of 1,1,2,2-tetrachloroethane as well Guengerich et al. 1991).

Both dichloro- and trichloroacetic acids are known to cause proliferation of peroxisomes (DeAngelo et al. 1986). In the work presented by Dow (1988), this property of the acid metabolites of 1,1,2,2-tetra

chloroethene was noted, and suggested as a possible mechanism by which the halocarbon could elicit hepatotoxic responses.

Toxification Mediated through Reduction. Paolini et al. (1992) investigated the reductive metabolism of 1,1,2,2-tetrachloroethane in mice. Those workers trapped a carbon-centered radical formed in vivo by reductive dehalogenation of 1,1,2,2-tetrachloroethane, a reaction presumably mediated by cytochrome P-450. Additionally, there was evidence of lipid peroxidation. These properties are reminiscent of the metabolism of carbon tetrachloride, where reductive formation of radical products leads to the stimulation of lipid peroxidation and its attendant hepatotoxic effects.

The hepatotoxic and/or carcinogenic effects of 1,1,2,2-tetrachloroethane probably result from the metabolism of that halocarbon by the cytochrome P-450 mixed function oxidase. Mechanisms may involve oxidative and reductive pathways that produce direct- (free radicals and/or acid chlorides) or indirect-acting (di- and trichloroacetic acids) toxins.

2.5 RELEVANCE TO PUBLIC HEALTH

Wide-scale production of 1,1,2,2-tetrachloroethane ceased decades ago. While a few reliable, limited, toxicokinetic and toxicological studies have been done, the majority of the studies available are not recent and do not always meet the standards for current-day data requirements. The chemical is present in hazardous waste sites, but no definitive epidemiological evaluation of the toxicological effects on humans living near such sites has been performed. Instead, only anecdotal reports of humans exposed to very large quantities of 1,1,2,2-tetrachloroethane, either accidentally or by suicide attempts, are available from which to draw conclusions regarding potential effects on humans.

The liver appears to be the target organ most likely to be affected from low-level 1,1,2,2-tetrachloroethane exposure. However, reliable studies which demonstrate the hepatotoxicity of 1,1,2,2-tetrachloroethane toxicity in animals or humans are few in number. 1,1,2,2-Tetrachloroetha is converted by the liver to reactive intermediates, and hepatic hyperplasia and necrosis are most often noted in human and animal exposures. Common to all volatile chlorohydrocarbons, 1,1,2,2-tetrachloroethane causes pronounced depression of the central nervous system, and respiratory depression is a frequent cause of death after acute-duration exposure to high doses.

2. HEALTH EFFECTS

The parent compound is volatile and is readily excreted by exhalation, either as the parent compound or as its metabolite, CO_2 While carbon-atoms derived from the parent may persist in the body, the sparse toxicokinetic data available suggest that this may occur largely from incorporation of those atoms into natural one- and two-carbon pools.

There is limited information available on the effects of 1,1,2,2-tetrachloroethane on reproduction. One report (Gohlke and Schmidt 1972) indicated necrosis and atrophy of the testes, disturbed spermatogenesis, and clumping of the sperm in rats after 120 days of oral exposure to 1,1,2,2-tetrachloroethane. However, there were serious limitations to this study. The NCI (1978) saw no histological changes in the reproductive organs of rats and mice receiving high doses (76-284 mg/kg/day) of the chemical for 78 weeks.

No investigations of developmental effects arising from inhalation, oral, or dermal exposures were available.

Currently, the major probable exposures to humans are those around hazardous waste sites, principally by inhalation exposure and by ingestion of contaminated drinking water. 1,1,2,2-Tetrachloroethane is activated to a proximate toxin by an enzyme system that is induced by prior exposure to ethanol, acetone, and other agents. Persons ingesting significant amounts of ethanol, or exposed to other solvents and chemicals that induce this system may be particularly susceptible to its toxic effects.

Minimum Risk Levels for 1 ,1,2,2-Tetrachloroethane.

Inhalation MRLs

No acute inhalation MRL has been derived for 1 ,1,2,2-tetrachloroethane due to inadequate data. No reliable inhalation studies are available that demonstrate a dose-response from acute exposure to 1,1,2,2-tetrachloroethane.

- An MRL of 0.4 ppm has been derived for intermediate-duration (15-364 days) inhalation exposure to 1,1,2,2-tetrachloroethane.

2. HEALTH EFFECTS

The intermediate-duration inhalation MRL is based on a LOAEL of 130 ppm for minimal hepatic effects in rats, using an uncertainty factor of 300 (3 for use of a minimal LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability). In the key study, 55 female Sprague-Dawley rats were exposed to 130 ppm 1,1,2,2-tetrachloroethane for 5 hours per day 5 days per week, for 15 weeks (Truffert et al. 1977). Liver, kidney, adrenal, genital, and lung pathologies were monitored and compared with controls. It was noted that this exposure resulted in increased liver/body weight ratios, and granulation and vacuolization in liver cells. Cellular changes regressed after 19 exposures and were no longer observed following the 39th exposure. Since these hepatic effects were reversible, were consistent with enzyme induction, and did not indicate a preneoplastic effect, they were considered to be "minimal." No significant changes were noted in the other tissues monitored. The major limitation of this study was that only one dose (130 ppm) was examined. However, there were no intermediate-duration inhalation studies with dose-response data that could be used to derive an MRL.

Existing 1,1,2,2-tetrachloroethane data are not considered suitable to derive an MRL for chronicduration inhalation exposure to 1,1,2,2-tetrachloroethane. The one available chronic inhalation study (Gobbato and Bobbio 1968) had variable exposure levels and no controls were used.

Oral MRLs

No acute oral MRL has been derived for 1,1,2,2-tetrachloroethane due to inadequate data. No reliable oral studies are available that demonstrate a dose-response from acute exposure to 1,1,2,2-tetrachloroethane.

- An MRL of 0.6 mg/kg/day has been derived for intermediate-duration (15-364 days) oral exposure to 1,1,2,2-tetrachloroethane.

The intermediate-duration oral MRL is based on a NOAEL value of 56 mg/kg/day for no-decrease in body weight gain in female rats in the 6-week study by NCI (1978). The NOAEL was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability). Groups of 5 male and 5 female Osborne-Mendel rats were administered 1,1,2,2-tetrachloroethane by gavage in corn oil 5 days per week for 6 weeks at doses of 56, 100, 178, 316, and 562 mg/kg/day. A 24% reduction in body weight gain was seen at 100 mg/kg/day in the female rats (LOAEL), with no

body weight effects noted at 56 mg/kg/day (NOAEL). In the male rats, a 38% reduction in body weight gain was noted at 178 mgfkglday. No body weight effects were noted in the same study in mice.

- An MRL of 0.04 mg/kg/day has been derived for chronic-duration (>365 days) oral exposure to 1,1,2,2-tetrachloroethane.

The chronic-duration oral MRL is based on a LOAEL value of 43 mg/kg/day for respiratory effects in female rats in the chronic study by NCI (1978). A LOAEL of 43 mg/kg/day was divided by an uncertainty factor of 1,000 (10 for use,of a LOAEL, 10 for extrapolation from animals to humans and 10 for human variability). Groups of 50 male and 50 female Osborne-Mendel rats were administered 1,1,2,2-tetrachloroethane by gavage in corn oil 5 days per week for 78 weeks. Males received doses of 62 or 108 mg/kg/day; females received doses of 43 or 76 mg/kg/day. Body weight gain was monitored, and gross and histological examination of the major organs and tissues was performed. Male rats exhibited labored respiration, wheezing, and nasal discharge at 62 mg/kg/day, while females showed the same symptoms at 43 mg/kg/day. Histological examination revealed no systemic effects in any organs examined, including the lungs and brain. In the same study, groups of mice similarly treated had renal effects at 284 mg/kg/day, consisting of tubular nephrosis leading to death in males and hydronephrosis in females, but not at 142 mg/kg/day. The toxicological significance of the clinical respiratory effects (labored respiration, wheezing, and nasal discharge) is unclear since no histological effects were observed. However, since clinical respiratory effects were also reported in human case reports (Sherman 1953; Ward 1955), these effects appear to be sufficient for the derivation of the MRL. No respiratory effects were found in mice. No other chronic-duration oral studies were located.

Death. Human deaths have occurred following excessive inhalation in the workplace or from dermal exposure from spilling a large amount of the chemical onto one's skin (Coyer 1944; Koelsch 1915; Willcox et al. 1915). 1,1,2,2-Tetrachloroethane has also caused death in humans when amounts more than 3 mL were ingested at one time (Hepple 1927; Mant 1953). Death in animals has also been reported following inhalation, oral, or ,dermal exposure to 1,1,2,2-tetrachloroethane (Dow 1988; Gohlke et al. 1977; NCI 1978; Price et al. 1978; Smyth et al. 1969).

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Systemic Effects.

Respiratory Effects. When administered by the inhalation or oral route, 1,1,2,2-tetrachloroethane has pronounced effects on the respiratory system, including irritation of the mucous membranes. Respiratory effects in humans have occurred only after exposures to what must have been very high concentrations of 1,1,2,2-tetrachloroethane (Mant 1953; Sherman 1953; Ward 1955). Present-day exposure standards preclude unintentional exposures to these levels of the chemical by humans, but accidental spills are still possible. Rats and guinea pigs experienced labored breathing at high vapor concentrations (Price et al. 1978).

Cardiovascular Effects. The general acute-duration effects of chlorinated hydrocarbons in depression of the central nervous system are manifested by low blood pressure and faint pulse in humans exposed to 1,1,2,2-tetrachloroethane by the inhalation, oral, and dermal routes (Coyer 1944; Mant 1953; Sherman 1953; Ward 1955; Willcox et al. 1915). No studies were located indicating deleterious cardiovascular effects in animals.

Gastrointestinal Effects. Gastrointestinal effects in humans can occur after inhalation or oral exposure. Nausea and vomiting were reported following inhalation exposure (Coyer 1944; Jeney et al. 1957; Lehmann and Schmidt-Kehl 1936; Lobo-Mendonca 1963). In addition to these effects, oral exposure causes irritation of the stomach mucosa and inflammation of the duodenum in humans (Elliot 1933; Forbes 1943; Hepple 1927; Lilliman 1949; Mant 1953).

Hematological Effects. Hematological effects, including reduced hemoglobin content, low white count, anemia, leukocytosis, leukopenia, and decreased hematocrit have been reported following inhalation or dermal exposure to humans (Coyer 1944; Horiguchi et al. 1964; Jeney et al. 1957; Minot and Smith 1921) and inhalation exposure to rats and monkeys (Horiuchi et al. 1962; Schmidt et al. 1972). However, these studies are quite limited due to their age and other factors, and thus the data are inconclusive -as to whether 1,1,2,2-tetrachloroethane will cause hematological effects in humans.

Musculoskeletal Effects. No studies were found on musculoskeletal effects of 1,1,2,2-tetrachloroethane administered by the inhalation, oral, or dermal routes in humans or animals.

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Hepatic Effects. The liver is an important target organ for 1,1,2,2-tetrachloroethane exposure. In humans, liver effects include jaundice and enlarged liver, and fatty accumulation in the liver (Coyer 1944; Minot and Smith 1921; Parmenter 1921; Willcox et al. 1915). Mice and rats commonly showed signs of hepatic necrosis and fatty degeneration of the liver (Dow 1988; Gohlke and Schmidt 1972; Horiuchi et al. 1962; Schmidt et al. 1980a, 1980b; Willcox et al. 1915). Liver damage has also been noted following intraperitoneal (Takeuchi 1966) and subcutaneous injections in mice (Plaa et al. 1958). The intraperitoneal or subcutaneous routes are only used for laboratory experiments on animals; humans would not be exposed by these routes. Mechanistic studies indicate that mammals can convert 1,1,2,2-tetrachloroethane to reactive metabolic intermediates that may damage the livers of the exposed animals.

Renal Effects. Swollen kidneys and convoluted tubules were observed in some humans acutely exposed orally and by inhalation (Elliot 1933; Hepple 1927; Willcox et al. 1915). Similarly, necrosis of the tubular cortex was reported in one study in rats exposed to oral doses for intermediate periods (Gohlke et al. 1977), and acute-duration inhalation produced interstitial nephritis in rats (Schmidt et al. 1980b). However, NCI (1978) reported no histopathological changes in the kidneys of rats exposed to higher doses of the chemical for 78 weeks, while male mice exposed to the highest dose died of tubular nephrosis and females experienced hydronephrosis. Thus, the data are inconclusive as to whether 1,1,2,2-tetrachloroethane will cause renal effects in humans.

Dermal Effects. In a dermal study, hyperemia and edema of the exposure site was observed in rabbits exposed acutely to undiluted 1,1,2,2-tetrachloroethane (Dow 1944).

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

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

2. HEALTH EFFECTS

Several investigators who measured body weight found no effects in animals (Horiuchi et al. 1962; Price et al. 1978; Schmidt et al. 1972, 1980b). Body weight losses after oral exposures not attributable to gastronomic disturbances have been seen in animals after acute-duration or longer exposures (Dow 1988; NCI 1978).

Immunological and Lymphoreticular Effects. There was one report of an enlarged and congested spleen in a case of intentional or accidental ingestion of 1,1,2,2-tetrachloroethane (Hepple 1927). Normal gross appearance of the spleen was reported by another investigator in an exposed patient (Elliott 1933). The limited data available from animal studies are inadequate to determine whether 1,1,2,2-tetrachloroethane will cause immunological effects in humans.

Neurological Effects. Humans exposed to high levels of 1,1,2,2-tetrachloroethane vapors (Lehmann and Schmidt-Kehl 1936) or who have accidentally consumed the chemical (Sherman 1953; Ward 1955) have become dizzy or even unconscious. Inhalation or oral exposure of animals has also resulted in such effects as narcosis, decreased motor activity, ataxia, and inhibition of learning (Dow 1988; Horvath and Frantik 1973; Pantelitsch 1933; Price et al. 1978; Wolff 1978). These studies indicate that 1,1,2,2-tetrachloroethane affects the central nervous system. However, the effects on the nervous system that have been described are general and non-specific.

Reproductive Effects. No studies were located regarding reproductive effects in humans following exposure to 1,1,2,2-tetrachloroethane. No effects were seen on the histology of the reproductive organs in female rats exposed by inhalation to 1,1,2,2-tetrachloroethane for 15 weeks (Truffert et al. 1977). Rats exposed orally to 1,1,2,2-tetrachloroethane were reported to have irreversible histological changes in the testes; however, this study has severe limitations and these changes were not observed in other studies (Gohlke et al. 1977). The effects that 1,1,2,2-tetrachloroethane might have on the reproductive capacity of humans are not known.

Developmental Effects. No studies were found on the developmental effects of 1,1;2,2-tetrachloroethane administered by the inhalation, oral, or dermal routes in humans. However, offspring of male rats exposed to 2 ppm 1,1,2,2-tetrachloroethane 4 hours per day during a 9-month period showed no gross malformations. There was no effect on the number of offspring per litter, neonatal body weight, viability of the offspring, or sex ratios on day 84 (Schmidt et al. 1972). In a study on the developmental effects of intraperitoneally administered 1,1,2,2-tetrachloroethane during gestation in

mice (Schmidt 1976), the chemical was found to have no effects at 300 mg/kg, while an increase in post-implantation losses was seen at 400 and 700 mg/kg. At 700 mg/kg, moderate effects on skeletal development were also seen, but no effects on fetal weight, number of resorptions, or number of pregnancies were observed. The authors considered 1,1,2,2-tetrachloroethane to be embryotoxic, but only weakly teratogenic, when given to animals via the intraperitoneal route. These studies provide little information on what developmental effects might occur in humans who are exposed to 1,1,2,2-tetrachloroethane in the air, water, or soil.

Genotoxic Effects. No studies were located regarding genotoxic effects in humans or animals following inhalation, oral, or dermal exposure to 1,1,2,2-tetrachloroethane.

In in *vitro* tests of genotoxicity, 1,1,2,2-tetrachloroethane has shown mixed results in assays for gene mutation, chromosomal aberration, DNA repair and synthesis, and cell transformation (see Table 2-4).

No studies were found that actually tested 1,1,2,2-tetrachloroethane for genotoxic effects in intact mature animals or humans, which would be more reliable predictors of human effects than in vitro experiments. Of the tests that used mammalian cells as indicators, the majority were negative. Of those using bacteria, yeast, or insects, about half yielded negative results. The probability that 1,1,2,2-tetrachloroethane may be genotoxic in mammalian cells is low, but existing evidence is insufficient to predict whether the chemical may pose a genotoxic threat to humans.

Cancer. It is questionable whether 1,1,2,2-tetrachloroethane will cause cancer in humans. An epidemiological study on the relationship between exposure to 1,1,2,2-tetrachloroethane and subsequent development of tumors in humans (Norman et al. 1981) showed a weak correlation between exposure to 1,1,2,2-tetrachloroethane and development of genital tumors and leukemia. However, the authors believed that other uncontrolled factors may have affected the results, so that no definite conclusions could be drawn from the study.

The ability of 1,1,2,2-tetrachloroethane to induce cancer in animals was tested in two bioassays. A study by the NCI (1978) looked for tumors in B6C3F$_1$ mice and Osborne-Mendel rats following oral administration of 1,1,2,2-tetrachloroethane for 78 weeks, followed by 32 weeks of observation. A second study focused on the development of pulmonary tumors in Strain A mice following intraperitoneal administration of 80-400 mg/kg/day of 1,1,2,2-tetrachloroethane for 2-6 weeks (Theiss

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

Species (test system)	End point	Result		Reference
		With activation	Without activation	
Yeast	Gene mutation	NT	+	Callen et al. 1980
Salmonella typhimurium	Gene mutation	–	–	Mitoma et al. 1984
		–	–	Nestman et al. 1980
		NT	+	Brem et al. 19074
Drosophilia	Gene mutation	NT	+	Woodruff et al. 1985; McGregor 1980
Chinese hamster ovary cells	Chromosomal aberrations	–	–	Galloway et al. 1987
Chinese hamster ovary cells	Sister chromatid exchange	+	+	Galloway et al. 1987
BALB/c 3T3 mouse cells	Cell transformation	NT	–	Little 1983; Tu et al. 1985
E. coli	DNA growth, repair or synthesis	NT	+	Rosenkrantz 1977; Brem et al. 1974
Rat hepatocytes		NT	–	Williams 1983
Mouse hepatocytes		NT	–	Williams 1983
Human embryonic intestinal cells		–	NT	McGregor 1980

NT = not tested; – = negative results; + = positive results.

et al. 1977). A highly significant increase in the incidence of hepatocellular carcinomas in mice in the NCI study was reported, while the rats had no significant increase in tumors at either site. However, an increased incidence of hepatocellular carcinomas in $B6C3F_1$ mice is not an unusual situation (Haseman 1984). Many chemicals increase the spontaneous rate of hepatocellular carcinomas in these mice, but do not produce tumors in other sites in mice or in rats. A marginally significant increase in pulmonary tumors in mice was reported at 400 mg/kg/day, but not at lower doses (Theiss et al. 1977).

Since the evidence for carcinogenicity in animals is restricted to one species, and the information from humans is inconclusive, 1,1,2,2-tetrachloroethane has been classified in Group C, as a "possible human carcinogen" by the EPA (IRIS 1994) and as Group 3 "not classifiable as to carcinogenicity in humans" by IARC (1987).

There is some information on a mechanism by which 1,1,2,2-tetrachloroethane may cause liver tumors in animals. 1,1,2,2-Tetrachloroethane was examined in a rat liver foci assay for its initiating and promoting potential for tumor production in male rats (Story et al. 1986). 1,1,2,2-Tetrachloroethane had no effects in the initiation protocol. The authors suggest that this lends support to the-hypothesis that 1,1,2,2-tetrachloroethane induces liver tumors primarily through a promoting mechanism.

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 (NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several

different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to 1,1,2,2-tetrachloroethane 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 1,1,2,2-tetrachloroethane 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 1,1,2,2-Tetrachloroethane

There currently are no specific biomarkers available to quantify exposure to 1,1,2,2-tetrachloroethane. However, metabolites of 1,1,2,2-tetrachloroethane, including trichloroacetic acid, trichloroethanol, and trichloroethanol glucuronide, may be measured in blood and urine (Breimer et al. 1974; Christensen et al. 1988; Koppen et al. 1988) (see Chapter 6). However, these metabolites are common to several types of chlorinated ethanes and would not be specifically indicative of exposure to 1,1,2,2-tetrachloroethane. Also, 1,1,2,2-tetrachloroethane is metabolized and excreted rather quickly, and the test might only indicate whether the person had been exposed within the last few days. If such a test of metabolite levels were available, the levels in the human body might be used to determine if adverse health symptoms were specifically the result of 1,1,2,2-tetrachloroethane exposure.

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

There currently are no biomarkers available to characterize effects caused by 1,1,2,2-tetrachloroethane. However, since 1,1,2,2-tetrachloroethane has the potential to cause liver damage at very high doses, it may be possible to correlate changes in urinary metabolites with serum indicators of liver malfunction, although the metabolites would not be specific for 1,1,2,2-tetrachloroethane.

2.7 INTERACTIONS WITH OTHER CHEMICALS

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

Alcohol, an inducer of cytochrome P-450 form IIEl, increased the metabolism (Sat0 et al. 1980) of 1,1,2,2-tetrachloroethane and intensified the effects of 1,1,2,2-tetrachloroethane in rats (Gohlke and Schmidt 1972). This indicates that humans who consume alcohol may be at increased risk for toxic effects from 1,1,2,2-tetrachloroethane. This is also the case for several other chlorinated aliphatic hydrocarbons. However, although alcohol combined with 1,1,2,2-tetrachloroethane increased the relative weight of the testes in rats (Schmidt et al. 1972), it did not alter the effects of 1,1,2,2-tetrachloroethane on the histopathology or function in the liver, nor was there damage to the kidneys, spleen, adrenals, brain, or thyroid.

Acetone pretreatment did not increase the severity of liver injury in rats given 1,1,2,2-tetrachloroethane. Additionally, rats given 1,1,2,2-tetrachloroethane in addition to 1,1-dichloroethylene or tetrachloroethylene exhibited a decrease in hepatotoxicity from animals given 1,1-dichloroethylene or tetrachloroethylene alone (Charbonneau et al. 1991).

2.8 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to 1,1,2,2-tetrachloroethane than will most persons exposed to the same level of 1,1,2,2-tetrachloroethane in the environment. Reasons

include genetic make-up, developmental stage, age, health and nutritional status (including dietary habits that may increase susceptibility, such as inconsistent diets or nutritional deficiencies), and substance exposure history (including smoking). These parameters result in decreased function of the detoxification and excretory processes (mainly hepatic, renal, and respiratory) or the pre-existing compromised function of target organs (including effects or clearance rates and any resulting endproduct metabolites). For these reasons we expect the elderly with declining organ function and the youngest of the population with immature and developing organs will generally be more vulnerable to toxic substances than healthy adults. Populations who are at greater risk due to their unusually high exposure are discussed in Section 5.6, Populations With Potentially High Exposure.

While no populations with unusual susceptibility to the health effects of 1,1,2,2-tetrachloroethane could be identified based on the available literature, the literature reviewed indicated that factors that increase the levels of the toxicating enzyme may be predicted to increase individual susceptibility. Those factors include chronic alcohol consumption, diabetes, and fasting (Soucek and Gut 1992).

2.9 METHODS FOR REDUCING TOXIC EFFECTS

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

2.9.1 Reducing Peak Absorption Following Exposure

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

professional, gastric lavage is suggested if it can be performed within minutes of the exposure to reduce the amount of absorbed solvent.

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

2.9.2 Reducing Body Burden

The body does not retain significant amounts of 1,1,2,2-tetrachloroethane. Currently, there is no recognized treatment to enhance elimination. The orthodox treatment for ingestion is entirely supportive. One potential method for enhancing elimination, however, is to increase the ventilation rate, thereby enhancing elimination via the lung. In a 6-year-old boy who had ingested 12-16 g of tetrachloroethylene, controlled hyperventilation over a 5-day period enhanced pulmonary excretion of the chemical (Koppel et al. 1985). This technique may be applicable to other volatile solvents like 1,1,2,2-tetrachloroethane.

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

2.9.3 Interfering with the Mechanism of Action for Toxic Effects

Clinical effects caused by acute 1,1,2,2-tetrachloroethane exposure include central nervous system depression, nephritis, and toxic hepatitis (HSDB 1994). Other effects include malaise, dizziness, fatigue, headache, and lightheadedness, all of which may disappear rapidly after the exposure ceases. The mechanism-of action for the central nervous system effects has not been clearly established, but it is probable that it is related to solvent effects on neuronal membranes exerted by many halogenated aliphatic hydrocarbons.

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

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

2.10 ADEQUACY OF THE DATABASE

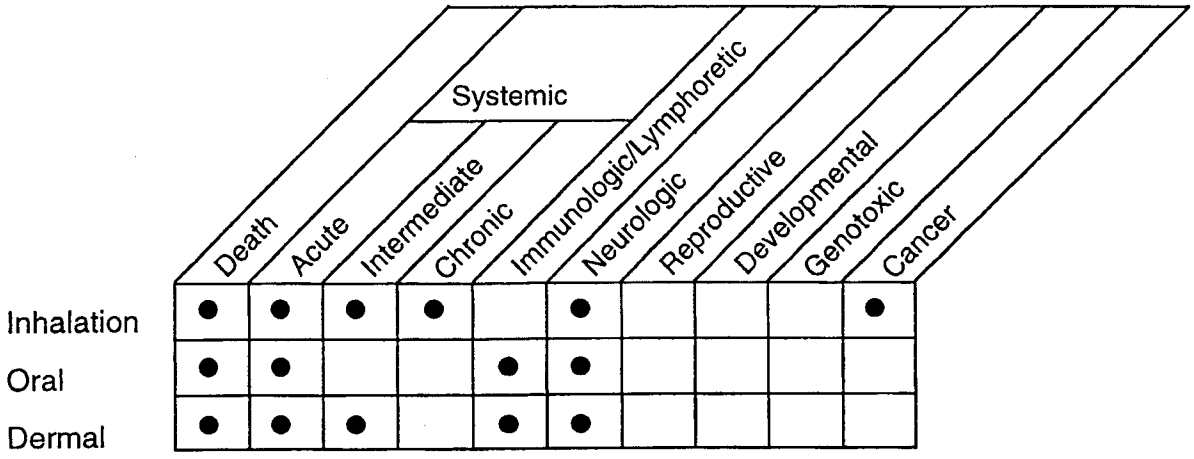
Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 1,1,2,2-tetrachloroethane is available. Where adequate information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

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

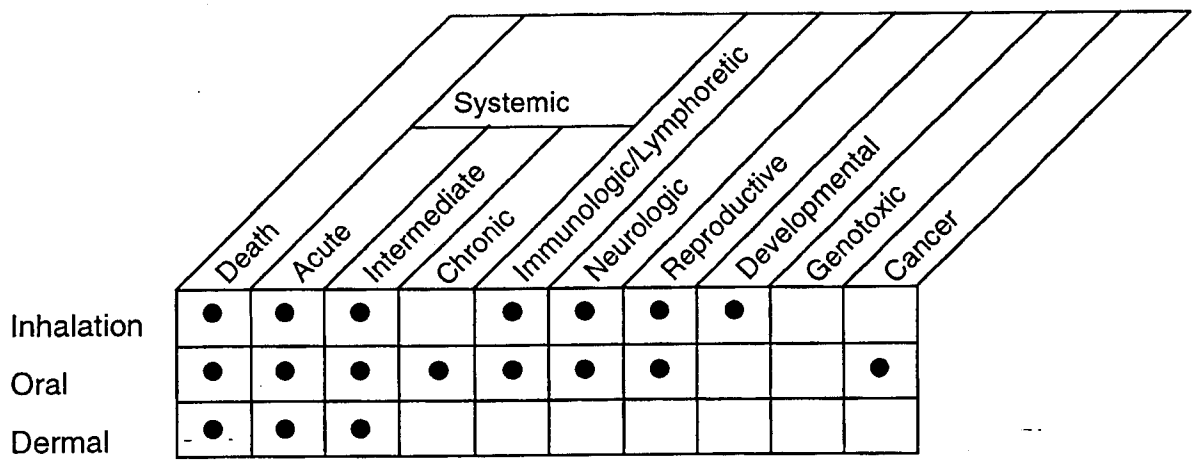
2.10.1 Existing Information on Health Effects of 1 ,I ,2,2-Tetrachloroethane

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to 1,1,2,2-tetrachloroethane are summarized in Figure 2-4. The purpose of this figure is to illustrate the existing information concerning the health effects of 1,1,2,2-tetrachloroethane. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing

Figure 2-4. Existing Information on Health Effects of 1,1,2,2-Tetrachloroethane



Human



Animal

● Existing Studies

information in this figure be interpreted as a "data need." A data need, as defined in ATSDR's Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

As seen in Figures 2-4, data exist for inhalation exposure of humans for death, systemic effects of acute-, intermediate-, and chronic-duration exposure, neurological effects, and cancer. A few human deaths have been reported following excessive inhalation exposure to 1,1,2,2-tetrachloroethane in occupational settings. Effects reported in humans exposed in the workplace consist of gastric distress including pain, nausea, vomiting, loss of appetite, and loss of body weight; increases in the number of white blood cells; jaundice, enlarged liver, liver degeneration, and cirrhosis; neurological symptoms such as headache, tremors, dizziness, numbness, and drowsiness; and possibly genital cancer and leukemia or lymphoma. In one experimental inhalation study, male volunteers experienced mucosal irritation, nausea, vomiting, and dizziness upon exposure to high levels of 1,1,2,2-tetrachloroethane. Data for oral exposure of humans consist mainly of case reports of suicidal or accidental ingestion of 1,1,2,2-tetrachloroethane, with data for death, systemic effects of acute-duration exposure, immunological/lymphoreticular and neurological effects. Autopsy findings in suicide cases included congestion and edema in the lungs and lung collapse, mucosal congestion of the esophagus and upper stomach, and epicardial and endocardial anoxic hemorrhage. In cases of humans accidentally given oral doses of 1,1,2,2-tetrachloroethane for parasite treatment, effects consisted of shallow breathing, pronounced lowering of blood pressure, and faint pulse during ensuing unconsciousness. One death was reported when a man cleaned up a 1,1,2,2-tetrachloroethane spill with his bare hands. Workers in India's bangle industry who dipped their hands in 1,1,2,2-tetrachloroethane, as well as inhaled it, had tremors, headache, and dizziness in addition to gastric disturbances. Mucosal irritation of the eyes has also been observed in humans exposed to 1,1,2,2-tetrachloroethane in air by direct contact of the concentrated vapor with the eyes.

For animals exposed by inhalation, data exist for death; systemic effects of acute- and intermediateduration; and immunological/lymphoreticular, neurological, reproductive, and developmental effects. Systemic effects consisted of labored respiration, hematological effects, and hepatic effects. Immunological effects consisted of a decrease in titer and an increase in the electrophoretic mobility of specific antibodies to typhoid in rabbits. Neurological effects included decreased motor activity, loss

of reflexes, ataxia, prostration, and narcosis. No reproductive or developmental toxicity was associated with inhalation exposure of animals. Data for oral exposure of animals exist for death; systemic effects of acute-, intermediate-, and chronic-duration exposure; immunological/lymphoreticular, neurological, and reproductive effects; and cancer. Systemic effects consisted of hepatic, thyroid, and adrenal effects, and decreases in body weight gain. Information on immunological/lymphoreticular effects is limited to histopathological effects on the spleen. Neurological effects consisted of central nervous system depression, debilitation, and decreased avoidance learning. An oral study in rats indicated an effect on spermatogenesis; however, the interpretation of the study was confounded by the fact that the rats had been maintained at a high temperature (35 °C). Cancer data consist of a significantly increased incidence of hepatocellular carcinoma in mice exposed orally. Existing data in animals exposed dermally to 1,1,2,2-tetrachloroethane are limited to an LD_{50} in rabbits; karyopyknosis and pseudoeosinophilic infiltration in guinea pigs; and eye closure, squinting, and lacrimation in guinea pigs and rats acutely exposed to the vapors.

2.10.2 Identification of Data Needs

Acute-Duration Exposure. Several studies are available regarding the effects of acute-duration exposures to 1,1,2,2-tetrachloroethane, both in humans (Coyer 1944; Hepple 1927; Lehmann and Schmidt-Kehl 1936; Sherman 1953; Ward 1955) and animals (Deguchi 1972; Dow 1988; Horiuchi et al. 1962; Price et al. 1978). These studies have identified the liver, central nervous system, and respiratory system as the major organ systems affected in both humans and animals following inhalation and oral exposure. However, the data were deemed insufficient to derive acute-duration inhalation or oral MRLs, since most of these studies are dated and are not designed with the same degree of scientific rigor as more recent studies. Well designed, recent studies are needed on acuteduration inhalation and oral exposure to 1,1,2,2-tetrachloroethane. Data for dermal exposure routes are limited, but this is not a primary route of human exposure for persons living near hazardous waste sites where 1,1,2,2-tetrachloroethane may be found.

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

are affected as those for acute-duration exposure. Controlled animal studies using the oral and inhalation routes and several concentrations of 1,1,2,2-tetrachloroethane support the findings of the human studies (Dow 1944; Gohlke et al. 1977; Horiuchi et al. 1962; NCI 1978; Schmidt et al. 1972, 1975; Truffert et al. 1977). Only limited intermediate-duration dermal exposures were studied in humans (Minot and Smith 1921) and rabbits (Dow 1944), but this is not a primary route of current human exposure. Inhalation exposure data are sufficient to derive an MRL of 0.4 ppm based on liver effects in rats (Truffert et al. 1977). However, only one dose was tested in this study; thus, well designed intermediate inhalation studies using several doses are needed to better understand the toxicity of 1,1,2,2-tetrachloroethane via inhalation exposure. An intermediate oral MRL of 0.6 mg/kg/day was calculated from a NOAEL based on body weight effects data in female rats (NCI 1978).

Chronic-Duration Exposure and Cancer. Limited data are available on effects of chronicduration exposure for the inhalation route in humans and animals. Insufficient inhalation data are available to derive a chronic inhalation MRL. The systemic effects of long-term repetitive oral exposure of mice and rats to 1,1,2,2-tetrachloroethane have been studied via gavage using several dose levels (NCI 1978). Contrary to shorter-duration experiments by other researchers, significant effects in the NCI studies were limited to the kidney in mice. Reexamination of these findings would help resolve this discrepancy. From this study, a chronic oral MRL of 0.04 mg/kg/day was calculated from a NOAEL based on respiratory effects in female mice (NCI 1978). Additional studies by more relevant routes of exposure, such as drinking water or feed, would be helpful to better define the toxicity of 1,1,2,2-tetrachloroethane via oral exposure.

There is one study on the possible carcinogenic effect of 1,1,2,2-tetrachloroethane on humans via inhalation exposure (Norman et al. 1981), and there are several oral studies of the effects on animals (NCI 1978; Theiss et al. 1977). The human study was inconclusive and in the NCI (1978) study, liver tumors were found in mice after long-term oral exposure. However, this species has a high rate of spontaneous incidence of these tumors, and this data may not be indicative of carcinogenic risk in humans. Theiss et al. (1977) injected 1,1,2,2-tetrachloroethane in mice, and found no increase in the number of lung tumors in mice receiving the low- and mid-level doses of 1,1,2,2-tetrachloroethane, while a marginally significant increase in lung tumors was seen in the high-dose group.

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Since humans are most likely to be exposed via the inhalation or oral routes, long-term animal studies using these routes would be useful. Studies that use a range of doses in several species and are able to identify a threshold for the non-cancer effects of this chemical would also be useful. There are no studies of the effect of chronic-duration dermal administration of 1,1,2,2-tetrachloroethane in humans or animals. Determination of the effect of chronic-duration dermal administration of 1,1,2,2-tetrachloroethane to animals would be methodologically problematic due to inadvertent oral and or inhalation exposures. Additionally, chronic-duration dermal exposure is unlikely for humans. Therefore, chronic-duration studies by this route are not recommended.

Genotoxicity. Information on the in vivo genotoxic effects of 1,1,2,2-tetrachloroethane is lacking for both humans and animals, although there are a number of *in vitro* tests of the mutagenicity of 1,1,2,2-tetrachloroethane (see Table 2-4). This type of data is not sufficient to determine if 1,1,2,2-tetrachloroethane is genotoxic in humans. *In vivo* testing and *in vitro* testing on human cell lines would help determine if 1,1,2,2-tetrachloroethane is genotoxic in humans. The known metabolism of 1,1,2,2-tetrachloroethane to reactive acid chlorides and/or free radical products suggests that genotoxic effects in humans and other mammals are possible.

Reproductive Toxicity. There were no human reproductive toxicity studies reported for 1 ,1,2,2-tetrachloroethane. Production of 1,1,2,2-tetrachloroethane has nearly ceased in this country, and it will probably not be possible to study reproductive effects associated with occupational exposure to this chemical. The effects of oral and inhalation exposures of various durations have been studied in animals. Atrophy of the seminal tubules was found after acute-duration inhalation (Schmidt et al. 1972) and after intermediate-duration ingestion in rats (Gohlke et al. 1977). However, conflicting data was provided by other workers. After acute-duration inhalation at 6,310 ppm, no effects on the testes, epididymes, ovaries, or uteruses were found in rats (Price et al. 1978). Similarly, an intermediateduration study by inhalation (Horiuchi et al. 1962) reported no effects on the testes in one monkey. Additionally, chronic-duration oral administration of 1,1,2,2-tetrachloroethane to rats and mice caused no increase in histological alterations in reproductive organs (NCI 1978). These conflicting results should be resolved by studies in animals using modern techniques and protocols for measuring adverse effects on reproductive parameters for both males and females.

Developmental Toxicity. There is only one study on the effects of inhalation or oral administration of 1,1,2,2-tetrachloroethane on development in humans or animals. In this intermediate-

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duration inhalation study, male rats were exposed to 1 ,I ,2,2-tetrachloroethane and mated with unexposed females, and the F_1 generation was observed for 12 weeks. No effects on the number of offspring per litter, neonatal body weight, offspring viability, or sex ratios were observed. No gross malformations in offspring were detected (Schmidt et al. 1972). Another animal study (Schmidt 1976) indicates that intraperitoneal injections of 1,1,2,2-tetrachloroethane into pregnant mice cause fetal abnormalities and resorptions. Well conducted animal studies, particularly by the inhalation and oral routes, are needed to determine the potential embryotoxicity, fetotoxicity, and teratogenicity of 1,1,2,2-tetrachloroethane.

Immunotoxicity. There is a lack of useful information on the effects of 1,1,2,2-tetrachloroethane on the immune system in humans, and the information available from animal studies in this area is very limited. The human studies were dated, lacked information on the dose received and duration of exposure, and reported only gross effects on the appearance of the spleen (Coyer 1944; Elliot 1933; Hepple 1927). Similarly, only superficial information on the effect of 1,1,2,2-tetrachloroethane on the spleen was provided in studies conducted in the rat (Gohlke et al. 1977; Schmidt et al. 1975) and monkey (Horiuchi et al. 1962). Since immunological end points are known to be very sensitive indicators of the toxicity of many chemicals, a battery of immunological function tests in animals would be helpful in clarifying whether 1,1,2,2-tetrachloroethane is an immunotoxicant.

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

Neurotoxicity. 1,1,2,2-Tetrachloroethane is known to have neurological effects on humans and animals exposed by the dermal, oral, and inhalation routes. The effects are related to generalized central nervous system depression and are similar across species and routes of administration. These include hyperactivity and excitability, giving way to narcosis, coma, ataxia, and prostration. These effects in humans are found after acute-duration inhalation (Lehmann and Schmidt-Kehlt936), intermediate-duration inhalation (Hamilton 1917; Horiguchi et al. 1964; Jeney et al. 1957), acute-duration oral administration (Sherman 1953; Ward 1955), and intermediate-duration dermal exposures (Lobo-Mendonca 1963; Minot and Smith 1921). For the most part, however, there was a lack of precise data on dose levels. Concomitant exposures to other solvents may have occurred. These effects were found in the rat (Gohke and Schmidt 1972; Horvath and Frantik 1973; Price et al. 1978;

Schmidt et al. 1975; Truffert et al. 1977), mouse (Lazarew 1929; Pantelitsch 1933), guinea pig (Price et al. 1978), cat (Lehmann 191 l), and monkey (Horiuchi et al. 1962) after acute- or intermediate-duration inhalation. Acute oral administration in rats also produced central nervous system depression and debilitation (Dow 1988). 1,1,2,2-Tetrachloroethane blocked avoidance learning when administered orally 30 minutes prior to testing (Wolff 1978). While it is assumed that these effects are those commonly found for volatile halocarbon solvents, there is no information about the specific site of action or mechanism of action in the nervous system.

Tests to show the site of action would be helpful in determining exactly how 1,1,2,2-tetrachloroethane affects the nervous system of humans. Also, a battery of neurofunction tests in animals would help identify the specific effects of the chemical and would evaluate the potential for long-term neurological effects in humans.

Epidemiological and Human Dosimetry Studies. An epidemiological study was conducted analyzing the cancer mortality of service men exposed to 1,1,2,2-tetrachloroethane during World War II (Norman et al. 1981). The exposure was presumed to be mostly by inhalation, but dermal exposure was also possible and precise dosimetry was unknown. Over one thousand subjects were used in each of the control and exposed groups. There were only very slightly elevated incidences (not statistically significant) of cancer of the genital organs, as well as leukemia and lymphoma. It is possible that humans who live near hazardous waste sites may be exposed to this substance in the air, water, and soil. Additional epidemiological studies examining neurological effects and effects on the liver and kidney would be helpful to better define the effects of chronic-duration low-level exposures to 1,1,2,2-tetrachloroethane in humans.

Biomarkers of Exposure and Effect.

Exposure. Since the metabolites of 1,1,2,2-tetrachloroethane are known, and can be measured in the urine of rats (Yllner-1971), it is possible to measure these metabolites in urine to see if a person has been exposed to 1 ,1,2,2-tetrachloroethane. However, these metabolites are common to several types of chlorinated ethanes and would not be specific for exposure to 1,1,2,2-tetrachloroethane. Also, 1,1,2,2-tetrachloroethane is metabolized and excreted rather quickly, and the test might only indicate whether the person had been exposed in the last few days. Measurement of parent compounds and

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metabolites in excreta or in biopsy samples (e.g., adipose), however, may allow quantitation of the body burden associated with exposures to known concentrations of 1,1,2,2-tetrachloroethane.

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

Absorption, Distribution, Metabolism, and Excretion. In both humans (Morgan et al. 1970; Lehmann and Schmidt-Kehl 1936) and laboratory animals (Dow 19SS), 1,1,2,2-tetrachloroethane is well absorbed after acute-duration inhalation exposure. While studies in which the quantitation of absorption following oral exposure was measured in humans were not available, the profound effects following ingestion of 1,1,2,2-tetrachloroethane indicate that appreciable amounts are absorbed by this route also. This is consistent with the data from animal studies, which indicate that oral doses are mostly absorbed (Milman et al. 1984; Mitoma et al. 1985). No studies were located regarding absorption following dermal exposure in humans. Only limited information was found regarding the distribution of 1,1,2,2-tetrachloroethane following inhalation, oral, or dermal exposure in humans and animals. High levels of binding of 1,1,2,2-tetrachloroethane equivalents to hepatic proteins were found in rats and mice following oral dosing. 1,1,2,2-Tetrachloroethane is extensively metabolized in animals and excreted chiefly as metabolites in urine and breath (Ikeda and Ohtsuji 1972; Mitoma et al. 1985; Yllner 1971).

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

pathways, would provide the information to fully characterize the pharmacokinetics of 1,1,2,2-tetrachloroethane in animals.

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

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

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2.10.3 Ongoing Studies

1,1,2,2-Tetrachloroethane has been approved for toxicity and carcinogenicity testing by NTP (1988). The prechronic study has been completed, and is currently under review to determine whether further studies will be carried out. No ongoing biomonitoring studies were identified. No ongoing studies on the toxicokinetics of 1,1,2,2-tetrachloroethane were identified.

3. CHEMICAL AND PHYSICAL INFORMATION

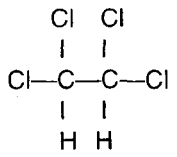
3.1 CHEMICAL IDENTITY

Information regarding the chemical identity of 1,1,2,2-tetrachloroethane is located in Table 3.1

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of 1,1,2,2-tetrachloroethane is located in Table 3-2.

Table 3-1. Chemical Identity of 1,1,2,2-Tetrachloroethane

Characteristic	Information	Reference
Chemical name	1,1,2,2-Tetrachloroethane	CAS 1994; HSDB 1995
Synonym(s)	Acetylene tetrachloride; sym-Tetrachloroethane; s-Tetrachloroethane; Tetrachloroethane; 1,1-Dichloro-2,2-dichloroethane	CAS 1994; SANSS 1994
Registered trade name(s)	Bonoform; Cellon; Westron	CAS 1994; RTECS 1994; HSDB 1995
Chemical formula	$C_2H_2Cl_4$	CAS 1994
Chemical structure		SANSS 1994
Identification numbers:		
CAS registry	79-34-5	CAS 1994; HSDB 1995
NIOSH RTECS	KI8575000	HSDB 1995
EPA hazardous waste	U209	RTECS 1994; HSDB 1995
OHM-TADS	8100014	HSDB 1995
DOT/UN/NA/IMCO shipping	1,1,2,2-Tetrachloroethane; UN 1702; IMO Class 6.1, poisons 6.1	NLM 1994
HSDB	123	HSDB 1995
NCI	CO3554	RTECS 1994

CAS = Chemical Abstracts Service; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; HSDB = Hazardous Substances Data Bank from National Library of Medicine; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; NLM = National Library of Medicine; OHM-TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances; SANSS = Structure and Nomenclature Search System

Table 3-2. Physical and Chemical Properties of 1,1,2,2-Tetrachloroethane

Property	Information	Reference
Molecular weight	167.85	Riddick et al. 1986; Lide 1993
Color	Colorless	Hawley 1981
Physical state	Liquid	Hawley 1981
Freezing point	-43.8 °C -36 °C	Riddick et al. 1986 Lide 1993
Boiling point	145.1 °C 146.2 °C 146.5 °C	Riddick et al. 1986 Lide 1993 Merck 1989
Density at 20 °C	1.594 1.595	Riddick et al. 1986 Lidde 1993
Odor	Sweetish, suffocating, chloroform-like; pungent	Hawley 1981; HSDB 1995; Merck 1989
Odor threshold:		
Water	0.50 ppm	Amoore and Hautala 1983; HSDB 1995
Air	1.5 ppm 3–5 ppm (21–35 mg/m^3)	Amoore and Hautala 1983 HSDB 1995
Solubility:		
Water	2.87 g/L (20 °C) 2.86 g/L (25 °C)	Riddick et al. 1986 Merck 1989
Organic solvent(s)	Miscible with ethanol, methanol, ether, acetone, benzene, petroleum, carbon tetrachloride, chloroform, carbon disulfide, dimethyl formamide, oils	Hawley 1981; HSDB 1995; Merck 1989
Partition coefficients:		
Log K_{ow}	2.39	Hansch and Leo 1985
Log K_{oc}	1.66 2.78	Chiou et al. 1979 ASTER 1995
Vapor pressure	5.95 mm Hg (25 °C) 9 mm Hg (30 °C)	Riddick et al. 1986 HSDB 1995; Flick 1985
Henry's law constant	4.7×10^{-4} atm-m^3/mol 4.55×10^{-4} atm-m^3/mol 1.80×10^{-3} atm-m^3/mol	Mackay and Shiu 1981 HSDB 1995 ASTER 1995
Autoignition temperature	No data	
Flash point	None, nonflammable	Hawley 1981; HSDB 1995
Flammability limits	Nonflammable	HSDB 1995

Table 3-2. Physical and Chemical Properties of 1,1,2,2-Tetrachloroethane (continued)

Property	Information	Reference
Conversion factors		
ppm to mg/m^3 in air (20 °C)	1 ppm = 6.98 mg/m^3	calculated
mg/m^3 to ppm in air (20 °C)	1 mg/m^3 = 0.14 ppm	calculated
Explosive limits	No data	

HSDB = Hazardous Substance Data Bank

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

4.1 PRODUCTION

1,1,2,2-Tetrachloroethane as an end-product was formerly produced in the United States only by the Specialty Materials Division of Eagle-Picher Industries in Lenexa, Kansas (SRI 1988). By the late 198Os, this facility had been sold to the Vulcan Materials Company, and production was discontinued at the Kansas facilities (Montgomery and Welkom 1990; SRI 1993). Since the late 1980s no production figures can be found. Approximately 440 million pounds (199.5 million kg) of 1,1,2,2-tetrachloroethane were produced in the United States in 1967 (Konietzko 1984). Production declined markedly thereafter, falling to an estimated 34 million pounds (15.4 million kg) by 1974.

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

1,1,2,2-Tetrachloroethane can be produced by the catalytic addition of chlorine to acetylene (HSDB 1996; IARC 1979); it may also be produced by the direct chlorination or oxychlorination of ethylene (Archer 1979). In most cases 1,1,2,2-tetrachloroethylene was not isolated to form an end-product, but was immediately thermally cracked to yield desired chemicals such as trichloroethylene, tetrachloroethylene, and 1,2-dichloroethylene (Archer 1979). 1,1,2,2-Tetrachloroethane may be produced as a byproduct in the manufacture of chemicals such as trichlorethylene from acetylene (HSDB 1994). Section 4.3 summarizes information on several chemicals in which 1,1,2,2-tetrachloroethane can appear as a trace constituent.

Table 4-l lists the facilities in each state that process 1,1,2,2-tetrachloroethane, the intended use, and the range of maximum amounts of 1,1,2,2-tetrachloroethane that are stored on site. Current production is for on-site uses or as a by-product, so that the phrase "manufacture" in the table heading does not imply production for sale as a commercial end-product. The data listed in Table 4-l are derived from the Toxics Release Inventory (TRI) and refer to facilities operating in 1993 (TR193 1995). Only

Table 4-1. Facilities That Manufacture or Process 1,1,2,2-Tetrachloroethane

Facility	Location[a]	Range of maximum amounts on site in pounds	Activities and uses
WESTLAKE MONOMERS CORP.	CALVERT CITY, KY	100,000-999,999	Produce; For on-site use/processing; As a reactant
VULCAN MATERIALS CO.	GEISMAR, LA	10,000-99,999	Produce; For on-site use/processing; As a by-product; As a reactant
BORDEN CHEMICALS & PLASTICS	GEISMAR, LA	1,000-9,999	Produce; For on-site use/processing; As an impurity; As a reactant
PPG IND. INC.	LAKE CHARLES, LA	1,000,000-9,999,999	Produce; As a by-product; As an impurity; As a reactant
VISTA CHEMICAL CO.	WESTLAKE, LA	1,000-9,999	Produce; As a by-product
FORMOSA PLASTICS CORP.	BATON ROUGE, LA	1,000-9,999	Produce; As a by-product; As an impurity
NA	LA	100,000-999,999	Produce; As a by-product
DOW CHEMICAL CO.	PLAQUEMINE, LA	100,000-999,999	Produce; As a by-product; As a reactant; Ancillary uses
MERCK & CO. INC.	RAHWAY, NJ	10,000-99,999	As a chemical processing aid
HARRELL IND. INC.	ROCK HILL, SC	10,000-99,999	As a formulation component; In repackaging only
TENNESSEE EASTMAN DIV.	KINGSPORT, TN	10,000-99,999	As a formulation component
DOW CHEMICAL CO.	FREEPORT, TX	1,000,000-9,999,999	Produce; For on-site use/processing; As a by-product; As an impurity; As a reactant
FORMOSA PLASTICS CORP.	POINT COMFORT, TX	10,000-99,999	Produce; As a by-product; As an impurity
OCCIDENTAL CHEMICAL CORP.	DEER PARK, TX	10,000-99,999	Produce; As a by-product
OCCIDENTAL CHEMICAL CORP.	GREGORY, TX	1,000-9,999	Produce; As a by-product

Source: TRI93 1995

[a] Post office state abbreviations used

NA = not available

certain types of facilities are legally required to report, and therefore, this is not an exhaustive list. Based on the information in Table 4-1, there are 15 facilities that reported having some on-site generation of 1,1,2,2-tetrachloroethane, with estimates for the amounts stored on-site as a by-product, chemical intermediate, or impurity showing extremely large differences among different facilities (TR193 1995).

4.2 IMPORT/EXPORT

Limited data pertaining to the import or export of 1,1,2,2-tetrachloroethane were located in the available literature. Imports in 1982 totaled 65,500 kg (HSDB 1996). Present tariff-setting and record-keeping practices combine 1,1,2,2-tetrachloroethane with other chemicals (USITC 1994). Because there is no end-product production or uses of 1,1,2,2-tetrachloroethane, current import and export levels may be assumed to be negligible.

4.3 USE

In the past, the major use for 1,1,2,2-tetrachloroethane was in the production of trichloroethylene, tetrachloroethylene, and 1,2-dichloroethylene (Archer 1979). It was also used as a solvent, in cleaning and degreasing metals, in paint removers, varnishes and lacquers, in photographic films, and as an extractant for oils and fats (Hawley 1981). Although at one time it could be used as an insecticide, fumigant, and weedkiller (Hawley 1981), it presently is not registered for any of these purposes. It was once used as an ingredient in an insect repellent, but registration was canceled in the late 1970s. With the development of new processes for manufacturing chlorinated ethylenes, the manufacture of 1,1,2,2-tetrachloroethane as a commercially marketed end-product has steadily declined in the United States and now appears to have ceased (HSDB 1996). A similar trend is reported in Canada (CEPA 1993).

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

themselves toxic and are the subjects of separate ATSDR profiles. Information on the availability of ATSDR profiles is available through the Internet World Wide Web (ATSDR 1996).

- Trichloroethylene (TCE) is widely used in industry as a degreasing and cleaning solvent. It is also used in the manufacture of PVC and is a component in a variety of paints, lacquers, varnishes, and adhesives. It is a common carrier (a socalled inert ingredient) for insecticides and fungicides. TCE is quite soluble in water, and has been found in many groundwater supplies. Further information is available in ATSDR profile TP-9209 (ATSDR 1996).

- 1,1,2-Trichloroethane, which closely resembles the more widely used 1,1,1-trichloroethane, is the feedstock used to make 1,2-dichloroethene (DCE or vinylidene chloride) (see below). Further information is available in ATSDR profile TP-89/24 (ATSDR 1996).

- 1,2-Dichloroethene (DCE or vinylidene chloride) is used in various plastics, acrylic fabrics, backing materials, resins, and glues. 1,1,2-Trichloroethane is a feedstock used to make DCE. DCE is considered a hazardous air pollutant and could be of concern to people living near plants where it is manufactured. Further information is available in ATSDR profile TP-95/04 (ATSDR 1996).

- Tetrachloroethylene (perchloroethylene, PCE or PERC) is the most widely used dry cleaning solvent. It is also an important industrial degreasing agent. At least 300,000 tons are used each year in the United States. It is also used in homes as a spot remover, paint stripper, and cleaner, and in the textile industry for fabrics and rugs. It is a component of vinyl-coated asbestos-cement pipes used in large water mains. It is also used to make chlorofluorocarbons (CFCs). Further information is available in ATSDR profile TP-92/18 (ATSDR 1996).

- Vinyl chloride is the chemical used to make polyvinyl chloride (PVC), one of the most widely used plastics products. 1,1,2,2-Tetrachloroethane appears as a trace constituent in batches of vinyl chloride monomer. The waste by-products associated with the production of vinyl chloride may contain very high levels (up to 23% by weight) of 1,1,2,2-tetrachloroethane (CEPA 1993). Further information on vinyl chloride is available in ATSDR profile TP-92/20 (ATSDR 1996).

- 1,2-Dichloroethane or ethylene dichloride (EDC) is generated in the production of vinyl chloride. It has end-uses as an industrial solvent and was once used as a lead scavenger in leaded gasolines. The waste by-products associated with the production of EDC may contain very high levels (up to 23% by weight) of 1,1,2,2-tetrachloroethane (CEPA 1993). Further information on EDC is available in ATSDR profile TP-93/06 (ATSDR 1996).

- 1,1,1-Trichloroethane (or methyl chloroform) is one of the most commonly used solvents in the United States. It is also used in the manufacture of 1,2- dichloroethene (see above). Further information on 1,1,1-trichloroethane is available in ATSDR profile TP-9400 (ATSDR 1996).

4.4 DISPOSAL

1,1,2,2-Tetrachlorethane disposal should follow the Resource Conservation and Recovery Act (RCRA) regulations appropriate for halogenated organic compound (HOC) wastes, which are likely to contain greater than 1,000 ppm of HOCs (EPA 1988, 1989). Selection of an appropriate technology for waste treatment and disposal depends on the RCRA waste code number. RCRA defines five main categories of wastes. Waste code U209 is specifically assigned to 1,1,2,2- tetrachloroethane, but wastes containing 1,1,2,2-tetrachloroethane could be assigned to one or more of 25 halogenated organic wastes under the RCRA U and P waste series.

For these U and P series wastes, the EPA has proposed three treatment technologies as alternative Best Demonstrated Available Technology (BDAT) treatment standards: (1) wet air oxidation followed by carbon adsorption; (2) chemical oxidation followed by carbon adsorption; or (3) incineration of waste waters. The BDAT for these HOC waste types is incineration. Industrial boilers or furnaces that function like waste disposal incinerators (e.g., cement kilns) may also substitute the combustible wastes for their normal fuel stocks. However, EPA does not believe that fuel substitution is a viable alterative for the majority of class U ("off-spec" materials that may contain impurities or mixtures of other wastes) HOC products. Chapter 7 of this profile provides a comprehensive overview of federal or state laws and regulations related to 1 ,I ,2,2-tetrachloroethane.

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

- process waste from the production of certain chlorinated aliphatic hydrocarbons (containing chains of 1 to 5 carbons);

- distillation light ends, spent filters, and spent desiccant generated in the production of certain chlorinated aliphatic hydrocarbons;

- wastes from the production of ethylene dichloride, vinyl chloride, trichloroethylene, perchloroethylene, chlorine, and 1,1,1-trichloroethane; and

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

Only one of these categories of wastes (process waste from the production of chlorinated aliphatic hydrocarbons) has an EPA-prescribed treatment standard before land disposal. Such wastes must be treated by incineration to comply with the restrictions. The other waste categories have concentrationbased standards which must be achieved before being sent to a RCRA-permitted land disposal facility (EPA 1988). The waste streams generated from the manufacture of vinyl chloride and ethylene dichloride have been noted in studies in both the United States and Canada to contain high levels of 1,1,2,2-tetrachloroethane (CEPA 1993). These waste streams are currently treated to recover and recycle many types of organic products prior to incineration, but trace amounts of 1,1,2,2-tetrachloroethane will remain, contributing to atmospheric emissions during the incineration disposal process, even assuming rates of destruction in excess of 99% (CEPA 1993).

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

1,1,2,2-Tetrachloroethane is a synthetic chemical not known to occur naturally (IARC 1979). It has been used as a chemical intermediate in the production of chlorinated ethenes, as an industrial solvent and extractant, and in a few pesticide preparations. Its production as an end-product declined markedly after the late 1960s; by the early 1990s manufacture as an end-product ceased both in the United States and in Canada (CEPA 1993). Present sources of 1,1,2,2-tetrachloroethane are largely attributable to fugitive emissions or discharges when it is generated as a by-product and emissions or discharges stemming from its production and use as a chemical intermediate.

The major releases of 1,1,2,2-tetrachloroethane are to the atmosphere and surface water, with very small amounts now being land-applied. If released onto soil, some of the chemical would be expected to volatilize, with the remainder leaching into the subsurface soil profile and, possibly, groundwater. If 1,1,2,2-tetrachloroethane is released to surface water, part of it would volatilize, with the remainder dissolving in water where it would undergo degradation through hydrolysis. In groundwater, the major degradation processes involve anaerobic biodegradation and chemical hydrolysis. Chemical hydrolysis is very sensitive to pH and is much faster under basic or neutral conditions. Trichloroethylene is the major, if not the sole, product of chemical hydrolysis. Half-lives for chemical hydrolysis reported at neutral pHs range from 29 to 102 days. Biodegradation proceeds by dehydrodehalogenation; products of biodegradation include trichloroethylene, 1,2-dichloroethene, and the highly toxic vinyl chloride.

In the ambient air, the dominant process for removal of 1,1,2,2-tetrachloroethane is the reaction with photochemically generated hydroxyl radicals, with an estimated half-life of 53 days (Atkinson 1987). Older studies, based primarily on theoretical calculations combined with laboratory experiments, have suggested residence times in the lower atmosphere with half-lives greater than 2 years (HSDB 1996). Removal also should occur through washout by precipitation; however, most 1,1,2,2-tetraehloroethane removed by this mechanism will likely reenter the atmosphere by volatilization. Atmospheric degradation of 1,1,2,2-tetrachloroethane is slow enough to allow considerable dispersion from source areas both within and outside of the United States. Slow diffusion into the stratosphere will also occur. Releases to surface water will mostly be lost by volatilization with a half-life of around

6.3 hours (HSDB 1996; Thomas 1982). Theoretical considerations and experimental results indicate that adsorption to sediment and bioconcentration in fish will not be significant (Verschueren 1983).

The general population may be exposed to 1,1,2,2-tetrachloroethane by inhalation of contaminated air; however, evidence from monitoring data (Class and Ballschmiter 1986) suggests that exposure levels are extremely low. It is difficult to assess occupational exposures because data on current production and use are not available. A National Occupational Exposure Survey (NOES) by NIOSH through May 1988 estimates that 4,143 employees are potentially exposed to 1,1,2,2-tetrachloroethane in the United States (NOES 1991). Occupational exposures, while low, are primarily via inhalation and dermal contact.

1,1,2,2-Tetrachloroethane has been identified in at least 273 of the 1,430 current or former NPL hazardous waste sites (HazDat 1996). However, the number of sites evaluated for 1,1,2,2-tetrachloroethane is not known. The frequency of these sites can been seen in Figure 5-1.

5.2 RELEASES TO THE ENVIRONMENT

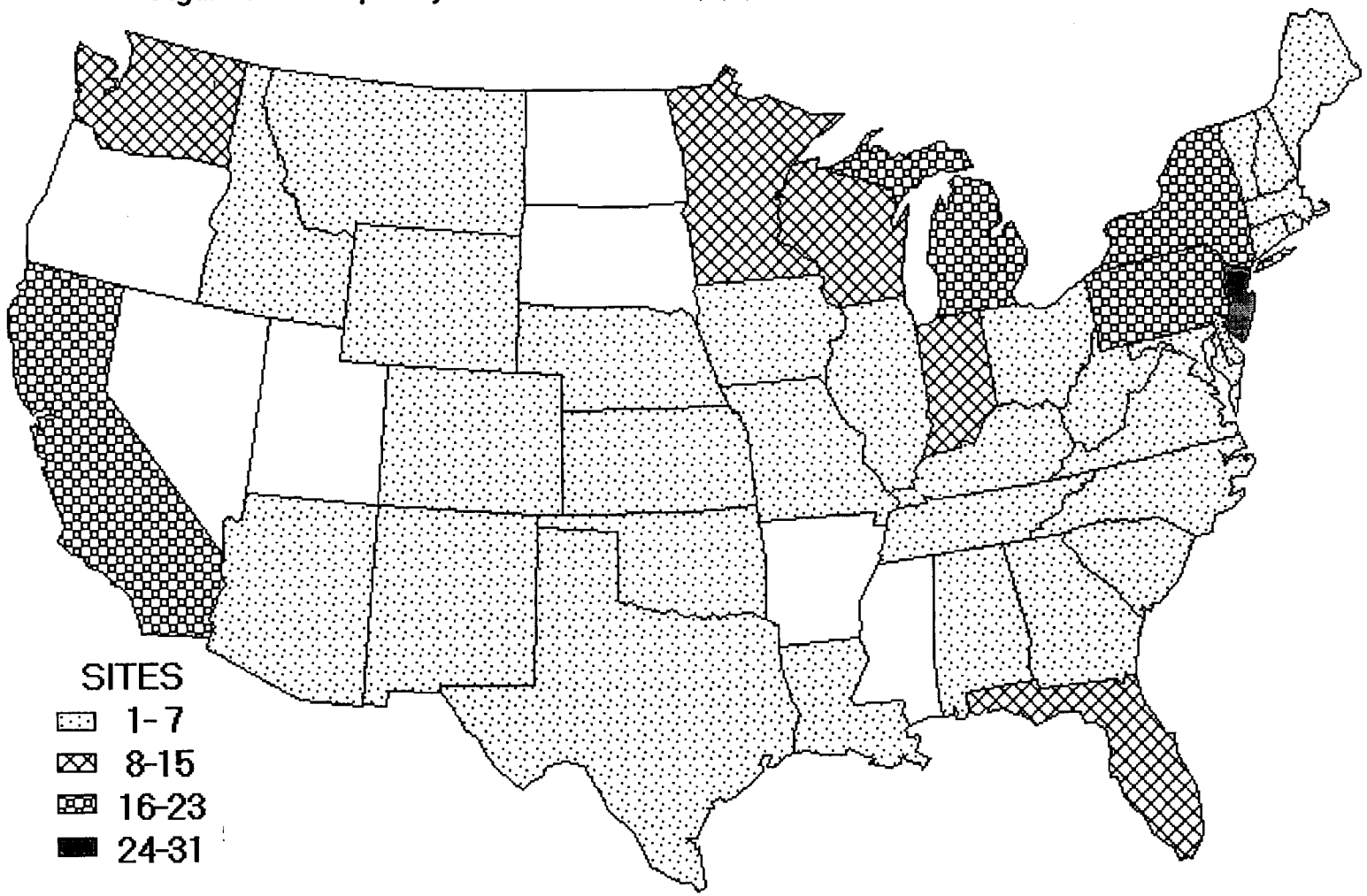
Table 5-1 lists releases to the environment from facilities that manufacture or process 1,1,2,2-tetrachloroethane. The data in Table 5-1 are derived from the Toxics Release Inventory (TRI) and refer to releases in 1993 (TR193 1995). Because only certain types of facilities are legally required to report, this list is not exhaustive. Of the 15 reporting facilities, 7 are located in Louisiana and 4 are located in Texas. The limited available data do not allow precise estimates of trends in releases to the various environmental media.

5.2.1 Air

1,1,2,2-Tetrachloroethane has been released into the air during the process of manufacturing trichloroethylene from acetylene or during use as a metal degreasing agent; as a paint, varnish, and rust remover; and as an extractant, solvent, and chemical intermediate (Verschueren 1983). It may also be emitted from hazardous landfills (Harkov et al. 1987).

1,1,2,2-Tetrachloroethane was one of the 10 most prevalent chlorinated chemicals found in solvent wastes that were incinerated each year prior to 1980 (Travis et al. 1986). A study was performed to

Figure 5-1. Frequency of NPL Sites with 1,1,2,2-Tetrachloroethane Contamination



Derived from HazDat 1996

Table 5-1. Releases to the Environment from Facilities That Manufacture or Process 1,1,2,2-Tetrachloroethane

State[b]	Number of facilities	Range of reported amounts released in pounds per year[a]						
		Air	Water	Land	Underground injection	Total environment[c]	POTW transfer	Off-site waste transfer
KY	1	90	0	0	0	90	0	11
LA	7	100-11600	0-520	0-1	0	100-12121	0	0-1566936
NJ	1	45	0	0	0	45	150	42000
SC	1	500	0	0	0	500	5	1500
TN	1	330	1	0	0	331	0	0
TX	4	0-13550	0-2400	0	0	0-15950	0	0-118835

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

ascertain the annual emissions of these chlorinated chemicals from a hypothetical 4,400 kw rotary kiln incinerator, with each chemical being represented according to its fraction in the stack of the incinerator. Annual stack emissions of 1,1,2,2-tetrachloroethane from such an incinerator were estimated to be 7.1 kg, assuming a standard destruction and removal efficiency of 99.99% and a waste throughput of $2.76x10^7$ kg/yr. Current information on incinerator-related generation of 1,1,2,2-tetrachloroethane could not be identified.

According to TR193 (1995) an estimated total of 28,203 pounds (12,820 kg) of 1,1,2,2-trichloroethane (amounting to 90.6% of the total environmental release) was discharged to air from manufacturing and processing facilities in the United States in 1993. These releases were associated with 15 manufacturing or processing facilities. The reported releases in 1993 were much lower than the 64,25 1 pounds (29,138 kg) in releases into the air reported in 1991 (TR191 1993). The TRI data (Table 5-1) should be used with caution since only certain types of facilities are legally required to report and, therefore, this list is not exhaustive.

5.2.2 Water

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

According to the TR193 (1995), an estimated total of 2,930 pounds (1,331 kg) of 1,1,2,2-trichloroethane (amounting to 9.1% of the total environmental release) was discharged to water from manufacturing and processing facilities in the United States in 1993. This would represent a very slight increase in the amounts released to water from 1991 when 2,102 pounds (953 kg) were reported as releases to water (TR191 1993). The TRI data (Table 5-l) should be used with caution since only certain types of facilities are required to report and, therefore, the list is not exhaustive.

5.2.3 Soil

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

during overland transportation. Many releases to soils and landfills may have involved mixed wastes containing small amounts of 1,1,2,2-tetrachloroethane along with other chemicals, which makes it virtually impossible to estimate overall release levels to the soil. Since it is volatile or can be readily transformed to such other compounds as TCE, 1,1,2,2-tetrachloroethane would not be expected to accumulate in sediments (HSDB 1996).

According to the TR193 (1995) only a single pound (0.4 kg) of 1,1,2,2-tetrachloroethane was discharged to soil from reporting facilities in the United States in 1993, amounting to less than 1% of the total releases to the environment. As noted above in Section 4.4, negligible levels of land disposal would be expected at present since RCRA discourages land disposal of 1,1,2,2-tetrachloroethane and similar halogenated wastes. The TRI data (Table 5-1) should be used with caution since only certain types of facilities are required to report and, therefore, the inventory is not an exhaustive list.

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

Most of the 1,1,2,2-tetrachloroethane that is released to the environment enters the atmosphere, where it is fairly stable in the lower atmosphere. Older research summarized in the Hazardous Substance Database (HSDB 1996) has suggested half-disappearance times of >2 years in the troposphere, while more recent studies suggest a half-life of approximately 53 days (Atkinson 1987). In either event, these residence times are long enough to allow atmospheric transport over large multi-state regions. Some of the 1,1,2,2-tetrachloroethane eventually will be transported to the stratosphere by processes such as diffusion, where it will then photodegrade rapidly. 1,1,2,2-Tetrachloroethane that is released into surface water will be lost by volatilization in a period of days to weeks. Based on a calculated Henry's law constant of 4.7×10^{-4} atm-m^3/mol (Mackay and Shiu 1981), the volatilization half-life of 1,1,2,2-tetrachloroethane (assuming first-order decay kinetics) from a model river 1 m deep flowing 1 m/set with a wind of 3 m/sec is estimated to be 6.3 hours (HSDB 1996; Thomas 1982). In waste water treatment plants that receive volatile compounds such as 1,1,2,2-tetrachloroethane from industrial discharges or other sources, air stripping is an important mechanism for transferring the chemical from the water into the air. Air stripping technologies involve cascading waste waters over trickling towers, the use of spray devices to convert the fluids into droplets or aerosols, and other techniques to increase the ordinary volatilization processes across liquid surfaces. In stripping, as opposed to ordinary

volatilization, the liquid and gas phases are dispersed. As a result, the interfacial surface area is much greater and liquid/gas mass transfer is greatly enhanced. Stripping, not biodegradation, was found to be responsible for removing 96% of the 1,1,2,2-tetrachloroethane in tests performed with activated sludge reactors (Kincannon et al. 1983). The half-disappearance time for 1,1,2,2-tetrachloroethane removal by stripping was 0.3 hour. In view of its moderate vapor pressure and low adsorptivity to soil, 1,1,2,2-tetrachloroethane would be expected to readily volatilize from soil surfaces.

The K_{OC} of 1,1,2,2-tetrachloroethane is 46 in a silt loam soil (Chiou et al. 1979). The partitioning to a soil poor in organic carbon soil removed less than 5% of the original 1,1,2,2-tetrachloroethane (Whitehead 1987). These results suggest that 1,1,2,2-tetrachloroethane will not adsorb appreciably to soil, suspended solids, and sediment.

The bioconcentration factor (BCF) of 1,1,2,2-tetrachloroethane in bluegill sunfish was found to be 8 in a 16day experiment (Barrows et al. 1980). This value is in reasonable agreement with bioconcentration factors of 21-36 estimated by regression analysis with K_{OW} ,(Veith et al. 1980). A bioconcentration factor of 2.0 for 1,1,2,2-tetrachloroethane in fathead minnows has been reported (ASTER 1995). Bioconcentration in fish is only considered to be significant when chemicals have BCF values greater than 500-1,000. Therefore, these results indicate that there is little tendency for 1,1,2,2-tetrachloroethane to bioaccumulate in fish and other aquatic organisms.

5.3.2 Transformation and Degradation

5.3.2.1 Air

1,2,2,2-Tetrachloroethane is nonreactive in the troposphere. Its primary reaction in the atmosphere is expected to be with photochemically produced hydroxyl radicals. The rate of this reaction has not been experimentally determined, but estimates of the rate can be made from structure-activity relations. Recent theoretical estimates of the atmospheric half-life (assuming first-order decay kinetics) of 1,1,2,2-tetrachloroethane as a result of its reaction with the average atmospheric concentration of hydroxyl radicals is 53.3 days (Atkinson 1987). Earlier research yielded estimates of a half-life for the reaction with photochemically produced hydroxyl radicals of >800 days, or <0.1% loss per 12-hour sunlit day (Singh et al. 1981). If 1,1,2,2-tetrachloroethane can be transported to the stratosphere, 1,1,2,2-tetrachloroethane will be photolyzed by ultraviolet light of shorter wavelength than available in

the troposphere to produce chlorine radicals (EPA 1979; Spence and Hanst 1978), which may react with ozone, thus affecting the stratospheric ozone layer. However, based on an estimated half-life and a tropospheric-to-stratospheric turnover time of 30 years (EPA 1979), it has been predicted that less than 1% of tropospheric 1,1,2,2-tetrachloroethane would eventually reach the stratosphere.

5.3.2.2 Water

1,1,2,2-Tetrachloroethane undergoes base-catalyzed hydrolysis in water at commonly encountered environmental pH values to form trichloroethylene (Cooper et al. 1987; Haag and Mill 1988). Investigators measured the hydrolysis rate over a range of pHs. The half-life at 25 "C and at pH 7.0 calculated from the second order rate equation in one study was 102 days (Cooper et al. 1987). The second study was conducted using solutions of a much lower ionic strength that is more typical of groundwater. Empirical half-disappearance times of 573 days at pH 6.05 and 36 days at pH 7.01 were obtained (Haag and Mill 1988). Similarly, researchers at Dow Chemical Company found that at ppm concentrations, 1,1,2,2-tetrachloroethane undergoes abiotic transformation to trichloroethylene in a sterile, anaerobic solution at pH 7.0 (Klecka and Gonsior 1983). By 28 days, 25% of the chemical had degraded. Hydrolysis of 1,1,2,2-tetrachloroethane was not affected by contact with the low-carbon aquifer materials associated with groundwater. 1 ,1,2,2-Tetrachlorethane in pore-water extracted from sediments showed a 29.1-day half-life at pH values between 7.0 and 7.5 (Haag and Mill 1988). In an anoxic sediment-water system (pH unreported) the half-life of 1,1,2,2-tetrachloroethane with both chemical hydrolysis and biotic degradation operative was 6.6 days (Jafvert and Wolfe 1987).

Results of aerobic biodegradability tests are conflicting. One study, in which 5 and 10 ppm of the chemical were incubated with sewage seed for 7 days, followed by 3 successive 7-day subcultures, found no significant degradation under aerobic conditions (Tabak et al. 1981). Other investigators obtained 41% degradation in 24 days in an unacclimated biodegradability test at an initial concentration of 4.4 ppm and no degradation in 5 days with an acclimated seed at an initial concentration of-0.85 ppm (Mudder and Musterman 1982). A 19% loss was obtained ina 5-day river die-away test using an acclimated system with an initial concentration of 17.3 ppm. None of the other chlorinated ethanes and ethenes in the study were found to be biodegradable. Many researchers,

however, would attribute most losses involved with sewage treatment to air-stripping processes and not biodegradation (Kincannon et al. 1983).

5.3.2.3 Sediment and Soil

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

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

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to 1,1,2,2-tetrachloroethane depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. In reviewing data on 1,1,2,2-tetrachloroethane levels monitored in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

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5.4.1 Air

Background levels of 1,1,2,2-tetrachloroethane measured in the troposphere have ranged from ≤0.1 to 0.4 ppt (Class and Ballschmiter 1986). Two air samples from rural areas of the United States did not contain detectable levels of the chemical (Brodzinsky and Singh 1982). In data collected in the late 1970s to early 1980s at 853 urban/suburban sites in the United States, the median sample concentration of 1,1,2,2-tetrachloroethane was 5.4 ppt, with values ranging from less than detection limits to a maximum of 4,800 ppt (Brodzinsky and Singh 1982). More information has subsequently been added to this database, bringing the sample size for 1,1,2,2-tetrachloroethane to 1,011 monitoring records (Shah and Heyerdahl 1988). With the addition of the new data, the overall median was computationally at or below the database lower detection limit value of zero; 75% of the samples showed concentrations less than or equal to 8 ppt. 1,1,2,2-Tetrachloroethane was infrequently found in the air of New Jersey cities; it was found in 9 of 38 samples in Newark, 1 of 37 samples in Elizabeth, and 4 of 35 samples in Camden in the summer of 1981 (Harkov et al. 1983), and in 4 out of 105 samples from the same 3 cities in the winter of 1982 (Harkov et al. 1987). Mean concentrations of 1,1,2,2-tetrachloroethane in major U.S. cities listed in other reports ranged from trace levels below detection limits to 57 ppb (Harkov et al. 1981, 1983; Lioy et al. 1985; Singh et al. 1981, 1982).

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

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

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The ranges of mean and maximum air concentrations of 1,1,2,2-tetrachloroethane in air at 5 NPL hazardous waste sites in New Jersey were 0.01-0.59 and 0.17-11.38 ppb, respectively, while the corresponding values for an urban landfill receiving municipal waste and non-hazardous industrial waste were 0.01 and 0.19 ppb (LaRegina et al. 1986). Samples of air surrounding the Kin-But waste disposal site near Edison, New Jersey contained up to 2.1 ppb of 1,1,2,2-tetrachloroethane. Air concentrations of 0.226 ppb of 1,1,2,2-tetrachloroethane were found in Iberville Parish, Louisiana along the Mississippi River, where many organic chemical production and storage facilities are located (Pellizzari 1982).

5.4.2 Water

Representative samples of surface water from New Jersey were analyzed during 1977-79 (Page 1981). These samples were collected from urban, suburban, and rural areas showing every type of land use common in the state. Sixty-seven of the 608 surface water samples (11%) contained 1,1,2,2-tetrachloroethane in concentrations as high as 3.0 ppb. Concentrations of 1,1,2,2-tetrachloroethane in United States surface waters reported in several studies range up to 9 ppb (EPA 1977, 1980d; Konasewich et al. 1978; Ohio River Valley Sanitation Commission 1980; Page 1976). In an analysis of ambient surface water data from EPA's national STORET database (Staples et al. 1985), samples with concentrations above detection limits were noted in 5% of the available samples, with the median 1,1,2,2-tetrachloroethane concentration being about 5.0 ppb.

Representative samples of groundwater from New Jersey were also analyzed during 1977-79 in a project summarized in Page (1981). Sixty-four of the 1,072 groundwater samples (6%) contained 1,1,2,2-tetrachloroethane, with concentrations as high as 2.7 ppb. 1,1,2,2-Tetrachloroethane has been detected in 10 private wells in Rhode Island at a concentration range of 1-2 ppb (RIDH 1989). An example of groundwater pollution by an industrial source is the case of an abandoned organic chemical manufacturing facility in Salem, Ohio that operated from 1961 to 1973 (Khourey et al. 1984). Maximum concentrations of 1,1,2,2-tetrachloroethane were 0.501-43.0 ppm in 5 on-site monitoring wells and 0.556 ppm in an off-site private well.

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

5. POTENTIAL FOR HUMAN EXPOSURE

There is limited information on the occurrence of 1,1,2,2-tetrachloroethane in ambient surface water or groundwater used as drinking water supplies for community water supply systems. A study of 30 Canadian public water treatment facilities did not show levels of 1,1,2,2-tetrachloroethane above a 1 ppb detection limit (Otson et al. 1982). In a United States Groundwater Supply survey, none of the 945 water supplies derived from tested groundwater sources contained 1,1,2,2-tetrachloroethane at the sensitivity limit of 0.5 ppb (Westrick et al. 1984). It was detected in 1 of 13 drinking water wells in Tacoma, Washington (Shilling 1985). It was not found in any of the 1,174 community wells and 617 private wells in a Wisconsin survey conducted in the early 1980s (Krill and Sonzogni 1986).

Analysis of ATSDR's HazDat database (HazDat 1996) shows that of 273 current and past NPL sites at which 1,1,2,2-tetrachloroethane was detected, 174 have 1,1,2,2-tetrachloroethane in groundwater.

5.4.3 Sediment and Soil

Limited information was located on general background levels of 1 ,1,2,2-tetrachloroethane in soils and sediments, with most studies focusing on problems associated with the remediation of waste sites. In an analysis of test wells around RCRA disposal sites, 1,1,2,2-tetrachloroethane was documented at levels above detection limits at 25 of 479 sites from a national sample (Plumb 1991). At one waste disposal site in Pennsylvania (Sable and Clark 1984), the concentration of 1,1,2,2-tetrachloroethane in a soil sample was 2.4 ppm. In an analysis performed on sediment monitoring data from rivers, lakes, and other aquatic systems contained in EPA's national STORET database, less than 1% of the samples contained 1,1,2,2-tetrachloroethane levels above the detection limits (generally around 5 µg/kg) (Staples et al. 1985). Based on ATSDR's HazDat database (HazDat 1996), at least 47 of 273 current or past NPL sites with 1,1,2,2-tetrachloroethane contamination showed the chemical in soil or sediment media.

5.4.4 Other Environmental Media

The data on 1,1,2,2-tetrachloroethane in fish or other biotic tissue samples are very limited. HazDat (1996) indicates 1,1,2,2-tetrachloroethane was found in tissue samples from a fish at one NPL site in Ohio. This site is on the Ashtabula River watershed. Examination of EPA's Fish Consumption Advisory Database (EPA 1995a) showed an advisory in effect for all species of fish on the lower Ashtabula River. Such fish consumption advisories are issued by states if there is some concern over the management of risks from the public eating fish caught in rivers and other water bodies. While

the management of risks from the public eating fish caught in rivers and other water bodies. While the pollution issues in the Ashtabula River have led to cautionary warnings in the consumption of locally caught fishes, available information on bioconcentration factors summarized in Section 5.3.1 above does not suggest a tendency for 1,1,2,2-tetrachloroethane to bioconcentrate, biomagnify, or bioaccumulate in the tissues of fish or shellfish.

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The general population may be exposed to 1,1,2,2-tetrachloroethane in ambient air, by ingesting contaminated drinking water, or upon dermal exposure to contaminated soil. Since concentrations of 1,1,2,2-tetrachloroethane in drinking water in broadly based surveys have been at or below detection limits, the level to which the general population is exposed appears to be very low. While 1,1,2,2-tetrachloroethane levels in ambient air are generally low, exposures are possible in areas around incinerators or cement kilns. Modeling estimates were made of 1,1,2,2-tetrachloroethane exposure due to inhalation and ingestion of contamination produced by incinerating chlorinated solvent waste at incinerator facilities at sites in southern California, the central Midwest, and the northern Midwest (Travis et al. 1986). For the California site, the average individual inhalation and ingestion intake was 774 and 285 μg/year, respectively. While food intake accounted for 27% of the total individual dose at the California site. this contribution was 60 and 65% for the 2 Midwestern sites.

A National Occupational Exposure Survey (NOES) conducted by NIOSH from 1981 to 1983 estimates that 4,143 workers are potentially exposed to 1,1,2,2-tetrachloroethane in the United States (NOES 1991). Of these estimated exposures, 3,665 were in occupations involving work in chemical research and development laboratories with the other exposures involving jobs in industrial chemical plants. The estimate is provisional since all the data for trade name products which may contain 1,1,2,2-tetrachloroethane have not been analyzed. The NOES study was based on field surveys of 4,490 facilities and was designed as a nationwide survey based on a statistical sample of virtually all workplace environments in-the-united States where 8 or more persons are employed (based on all Standard Industrial Classification (SIC) code workplace types except mining and agriculture) (Sieber et al. 1991). The NOES database does not contain information on the frequency, concentration, or duration of exposure; the survey provides only estimates of workers potentially exposed to chemicals in the workplace.

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According to OSHA (1991), the current S-hour TWA permissible exposure level for 1,1,2,2-tetrachloroethane is 1 ppm. According to NIOSH (1992), the recommended exposure level for a I0-hour TWA is 1 ppm (7 mg/m^3) 1,1,2,2-tetrachloroethane.

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Exposures are possible for individuals living near waste disposal facilities where 1,1,2,2-tetrachloroethane site contamination has occurred. Higher inhalation exposures would also occur in workers at petrochemical plants where 1,1,2,2-tetrachloroethane is still used as a chemical intermediate. Other populations with higher exposures would include people living close to NPL or other waste sites where leachates or runoff from contaminated soils could affect groundwater used for drinking water. In at least one instance, pollution from a large NPL site in Ohio has resulted in a fish consumption advisory for local recreational and subsistence fishers.

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 1,1,2,2-tetrachloroethane 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 1,1,2,2-tetrachloroethane.

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

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5.7.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of 1,1,2,2-tetrachloroethane are well characterized and allow prediction of the environmental fate of the compound (see Table 3.2). No additional studies are required at this time.

Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1991, became available in May of 1992. This database will be updated yearly and should provide a list of industrial production facilities and emissions. Currently, reports based on TRI (EPA 1995b) provide virtually the only source of quantitative information on production levels or release levels to the environment (as a by-product or chemical intermediary) for 1,1,2,2-tetrachloroethane. Additional mechanisms to supplement this TRI information rank as a major data need.

Production methods and uses for 1,1,2,2-tetrachloroethane are documented (Archer 1979; HSDB 1996; IARC 1979), but there is no recent detailed breakdown of the percentage of production consumed by each use category. Figures on current exports are also lacking. Approximately 440 million pounds (199 million kg) of 1,1,2,2-tetrachloroethane were produced in the United States in 1967 (Konietzko 1984). Production declined markedly thereafter, falling to an estimated 34 million pounds (15 million kg) by 1974. While 1,1,2,2-tetrachloroethane is apparently no longer produced as a final product, it may occur as a chemical intermediate or waste product in the manufacture of other chemicals (CEPA 1993; HSDB 1996). Better quantitative measures of current production, including production for export, is a data need for estimating the potential for environmental releases from various industries, as well as potential concentrations in the environment. Knowledge of which consumer products contain 1,1,2,2-tetrachloroethane is also a data need for estimating general population exposure. Unfortunately, this type of detailed information is difficult to obtain since companies consider it to be confidential info-ormation. While monitoring information on discharges was gathered during the 1970s and early 1980s when the EPA was developing criteria and effluent guidelines for a number of priority pollutant toxics (Shackelford et al. 1983), the Toxics Release Inventory now constitutes the only major broad-based survey of releases to the environment. According to the most recent TRI information (TR193 1995), releases to the air and water still continue from processing facilities in the United

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States. At present, the TRI data only cover major industrial sectors, so some releases may go unreported. Possible expansions of the types of facilities required to submit information under the TRI reporting requirements could help make this source of information more comprehensive.

While regulatory coverage for halogenated organic wastes has become increasingly more well defined (EPA 1989), record keeping under RCRA procedures works best when a chemical is a major constituent in a waste. Since 1,1,2,2-tetrachloroethane is now usually a minor component in other waste materials, there is often little documentation of the amounts of 1,1,2,2-tetrachloroethane entering waste disposal sites. Since 1,1,2,2-tetrachloroethane is still encountered at 273 of 1,430 current or past NPL sites (HazDat 1996), better quantitative estimates of amounts entering active disposal sites would be a legitimate data need.

Environmental Fate. 1,1,2,2-Tetrachloroethane is quite volatile; but the highest potential for persistent pollution is when the chemical has been introduced into sediments and groundwater (Atkinson 1987; HSDB 1996; Mackay and Shiu 1981). While the chemical can be biodegraded under anaerobic conditions (Bouwer and McCarty 1983), there are major differences under aerobic conditions (Tabak et al. 1981). Further investigation would be helpful to resolve the discrepancies in the aerobic degradation data for 1,1,2,2-tetrachloroethane and would rank as a major data need.

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

Food Chain Bioaccumulation. Given its tendency to either volatilize to the atmosphere (Atkinson 1987; HSDB 1996; Mackay and Shiu 1981) or become transformed into such other chemicals as TCE (Cooper et al. 1987; Haag and Mill 1988), 1,1,2,2-tetrachloroethane shows little potential for bioaccumulation. While there are some minor discrepancies between observed bioconcentration factors (Barrows et al. 1980) and estimates predicted from regression analyses

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(ASTER 1995; Veith et al. 1980), 1,1,2,2-tetrachloroethane shows no significant tendency to bioconcentrate and is not considered to show significant potential to bioaccumulate in food chains. No major data needs are apparent for this information category.

Exposure Levels in Environmental Media. In studies based on monitoring data from the late 1970s and early 1980s, 1,1,2,2-tetrachloroethane concentrations in receiving waters (primarily rivers) of at least 10 ppb were documented in approximately 10% of the samples collected in a national study of runoff from urban areas, with a maximum reported concentration of 1,400 ppb (Cole et al. 1984). In soils and sediments, information from NPL sites shows detections at 273 of 1,430 sites. Since the treatment, storage, and distribution processes used in large community drinking water systems will generally release volatile chemicals to the air, 1,1,2,2-tetrachloroethane concentrations in public drinking water are generally very low. The chemical has been detected in untreated groundwater formations used for private wells in some parts of the country (Page 1981; RIDH 1989). The highest levels have been found in groundwater in the vicinity of waste disposal sites (Khourey et al. 1984). Background levels of 1,1,2,2-tetrachloroethane in the air are typically less than 0.4 ppt (Brodzinsky and Singh 1982; Class and Ballschmiter 1986). Limited data collected in the vicinity of waste disposal sites has shown ambient air levels considerably higher (from >l ppb to as high as 2.1 ppb) (Gupta et al. 1984; LaRegina et al. 1986).

It is important to have recent data concerning the levels of this chemical in the atmosphere as well as in soils, sediment, groundwater, and surface water to determine background concentrations and exposure levels. Reliable monitoring data for the levels of 1,1,2,2-tetrachloroethane in contaminated media at hazardous waste sites are needed, so that the information obtained on levels of 1,1,2,2-tetrachloroethane in the environment can be used in combination with the known body burdens of 1 ,1,2,2-tetrachloroethane to assess bioavailability and potential risks of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. Information on exposure levels in humans is extremely limited, with most conclusions on health effects being based on inferences from animal studies (Yllner 1971). General population and occupations exposure levels have been based on models (Travis et al. 1986) or provisional estimation techniques (NOES 1991). Improved information on human exposure levels is therefore a data need. This information is necessary for assessing the need to conduct health studies on these populations.

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

5.7.2 Ongoing Studies

No information was found to indicate that there are studies in progress that relate to the environmental fate of 1,1,2,2-tetrachloroethane (FEDRIP 1995). Similarly no ongoing monitoring or exposure studies were identified.

6. ANALYTICAL METHODS

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

This section summarizes the methods available for the analysis of 1,1,2,2-tetrachloroethane in biological and environmental media. In designing a study and choosing a method, it is very important that adequate attention be paid to the extent of validation and field applicability. Some of the methods have been validated (e.g., EPA 502), while some of the literature methods have not. It is the analyst's responsibility to determine the data quality needed before initiating the application of a particular method.

6.1 BIOLOGICAL MATERIALS

A few studies were found in the literature that report the determination of this compound in biological matrices. The discussion about the method that may be most sensitive for the determination of tetrachloroethane levels in environmental samples and the advantages and disadvantages of the commonly used methods (see Section 6.2) are also applicable to biological samples. Because of its higher boiling point and the possibility of its loss through chemical reactions (Yasuda and Loughran 1977), the recovery of this compound from complex biological samples by most analytical methods is expected to be lower than the recoveries from air and water samples. The analytical methods for the determination of 1,1,2,2-tetrachloroethane in biological matrices are given in Table 6-1. Information about methods for metabolites of 1,1,2,2-tetrachloroethane in animal samples is given in Section 6.3.1; these methods should be applicable to human samples.

Table 6-1. Analytical Methods for Determining 1,1,2,2-Tetrachloroethane in Biological Samples

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

Table 6-1. Analytical Methods for Determining 1,1,2,2-Tetrachloroethane in Biological Samples (continued)

Sample matrix	Sample preparation	Analytical method	Sample detection limit	Percent recovery	Reference
Blood, urine, tissues, consumer products	Tissue: Placement of 20–50 mg wet mass (removed while it is frozen) into 7 mL vial with internal standard and 1 mg Subtilisin A. Equilibration and analysis as for blood.	GC then split to both FID and ECD	No data	No data	Streete et al. 1992
Blood, urine, tissues, consumer products	Product: Analysis of headspace after placing small volume of product into vial.	GC then split to both FID and ECD	No data	No data	Streete et al. 1992

ECD = Electron Capture Detector; FID = Flame Ionization Detector; GC = Gas Chromatography; HRGC = High Resolution Gas Chromatography; HRMS = High Resolution Mass Spectrometry; MS = Mass Spectrometry

6. ANALYTICAL METHODS

Chen at al. (1993) have reported a method for 1,1,2,2-tetrachloroethane in blood and several types of tissue from rats. Samples were homogenized with saline and isooctane, and an aliquot of the isooctane was transferred to a sampling vial for headspaceigas chromatography (GC) analysis. Fairly low detection limits (400 ng/g) and good recoveries (90-100%) were reported. Another method for volatile compounds in blood, urine, and tissues that should be applicable to the analysis of 1,1,2,2-tetrachloroethane was reported by Streete et al. (1992). In this case, headspace analysis was used to determine 1,1,2,2-tetrachloroethane in blood, urine, and tissue (after treatment with a proteolytic enzyme). The authors stress the importance of collecting liquid samples in a container with no headspace and keeping tissue samples frozen until a 20-50 mg piece is placed into the headspacesampling vial. The most sensitive method found is based on purge and trap isotope dilution GC in conjunction with high resolution mass spectrometry (GC/HRMS). This method from the Centers for Disease Control and Prevention laboratory in Atlanta (Ashley et al. 1992) reported a limit of detection (LOD) for 1,1,2,2-tetrachloroethane in blood of 0.005 ppb with recoveries ranging from 116% at 0.063 ppb to 76% at 0.41 ppb. Great effort was devoted to the clean-up of collection and analysis equipment to make such LODs possible. Additional information about the mass spectrometric (MS) aspects of the method was reported by Bonin et al. (1992).

6.2 ENVIRONMENTAL SAMPLES

Methods for the analysis of 1,1,2,2-tetrachloroethane in environmental samples are presented in Table 6-2. There are two common methods used for the concentration of 1,1,2,2-tetrachloroethane from air. One is the direct collection of organics in a cryogenically cooled trap in line with a GC; the other method is concentration of the organic via adsorption on a sorbent column followed by thermal or solvent desorption. An advantage of the direct sampling approach is that it can be very simple. The disadvantages of the cryogenic cooling approach are that the method is cumbersome and that condensation of moisture from air may block the passage of further air flow through the trap. The sorbent-based concentration methods permit very large concentration factors and, as a result, good LODs. The disadvantages of sorbent tubes are that the sorption and desorption efficiencies may not be 100% (breakthrough during collection and poor recovery during analyte desorption) and that the background impurities in the sorbent tubes might elevate the method detection limit (Cox 1983). An additional problem with sorbent tubes is that analyte can be lost if the tube is improperly stored after sample collection. For example, Atlas and Schauffler (1991) reported losses for 1,1,2,2-tetrachloroethane of 50% when the charcoal sorbent tube was stored at room temperature for 2 days before

Table 6-2. Analytical Methods for Determining 1,1,2,2-Tetrachloroethane in Environmental Samples

Sample matrix	Sample preparation	Analytical method	Sample detection limit[a]	Percent Recovery	Reference
Air	Sample preconcentration in liquid oxygen-cooled trap	GC/ECD	<1 ppt (<6.98 ng/m^3)	=85	Singh et al. 1981
Breathing zone air	Sample collection by adsorption onto Tenax followed by thermal desorption	Cryofocussing HRGC-MS	No data	80–120	Krost et al. 1982 Hartwell et al. 1987
Air	Sample adsorption onto Tenax followed by thermal desorption	HRGC-ECD	0.1 ppt (0.698 ng/m^3) for 1 L	No data	Class and Ballschmiter 1987
Air	Preconcentration of analyte onto Tenax-GC followed by thermal desorption onto GC column (EPA Method TO1)	GC/MS	No Data	No data	EPA 1984b
Air	Collection of an aliquot of the air into a SUMMA passivated canister followed by pumping an aliquot of the air through a cryogenic trap to focus volatile organics; thermal desorption onto GC column (EPA Method TO14)	GC/MS (full scan or selected ion monitoring) GC/FID/ECD/PID	No data; depends on air aliquot size and mode of detection	No data; generally very good for non-polar volatile organics	EPA 1984c
Air	Preconcentration of analyte onto adsorbent trap containing 5 mg charcoal followed by immediate elution of traps with 30–50 μL of redistilled benzene in 3–5 aliquots	GC/ECD	Low parts per trillion in 20 L sample	85	Atlas and Schauffler 1991
Air	Passive collection onto carbon-based badge (3M OVM 3500); extraction with carbon disulphide containing internal standard	GC/MS (SIM)	< 1 μg/m^3 (0.14 ppb)	89.3	Otson et al. 1994
Air	Equilibration of air with polymer-coated fiber for analyte concentration followed by thermal desorption of fiber (Solid Phase Micro Extraction)	GC/MS	0.06 ppbv (1.5% RSD)	70–98 depending on how fiber is stored after collection	Chai and Pawliszyn 1995

Table 6-2. Analytical Methods for Determining 1,1,2,2-Tetrachloroethane in Environmental Samples (continued)

Sample matrix	Sample preparation	Analytical method	Sample detection limit[a]	Percent Recovery	Reference
Air	Direct injection of 1 mL air into GC and cryogenic focusing (-150 °C) of volatiles at head of 0.25 mm i.d. x 5 m column followed by rapid heating to +150 °C in 20 ms.	High speed GC/FID	2 ppb (14 $\mu g/m^3$) (depends on retention time)	No data	Mouradian 1991
Occupational air	Preconcentration of analyte from air onto solid sorbent tube (petroleum charcoal); desorption with CS_2 and injection of 5 μL into GC. Working range is 1.5–15 ppm (10 to 100 mg/m^3) for a 10 L air sample. (NIOSH Method 1019)	GC/FID	0.01 mg/sample (0.3 mg/m^3 for 30 L sample volume)	106	NIOSH 1994
Air from waste and landfill sites	Adsorption of analyte onto Tenax followed by thermal desorption	Cryofocussing HRGC-MS or HRGC-ECD	0.01–0.1 ppb (0.07–0.7 $\mu g/m^3$)	No data	Gianti et al. 1984 LaRegina et al. 1986
Treated and raw source water	Purge and trap followed by thermal desorption	GC/MS	<1.0 µg/L	90	Otson 1987
Treated and raw source water	Purging of sample and on-column trapping	GC/FID and GC/HECD	1 µg/L (FID) 0.5 µg/L (HECD)	24 (HECD)	Otson and Williams 1982
Finished drinking/ raw source water	Purge and trap onto Tenax/silica/ charcoal followed by thermal desorption	Subambient programmable HRGC-MS (EPA Method 524.1)	0.28–0.41 µg/L	111 at 1 µg/L	EPA 1986c
Finished drinking/ raw source water	Purge and trap onto Tenax/silica/ charcoal followed by thermal desorption	Cryofocussing (wide or narrow bore) HRGC-MS (EPA Method 524.2)	0.04 µg/L (wide bore), 0.20 µg/L (narrow bore)	91 at 0.4–10 µg/L (wide bore), 100 at 0.5 µg/L (narrow bore)	EPA 1986d

Table 6-2. Analytical Methods for Determining 1,1,2,2-Tetrachloroethane in Environmental Samples (continued)

Sample matrix	Sample preparation	Analytical method	Sample detection limit[a]	Percent Recovery	Reference
Finished drinking water, raw source water, or drinking water in any treatment stage	Purgihg of organics from water using inert gas and trapping onto a sorbent. Thermal desorption onto GC. (EPA Method 502.2)	GC/PID (10.0 eV nominal)/ELCD	0.01 µg/L with ELCD (no response from PID)	99 (6.8% RSD)	EPA 1988d
Drinking water, raw source water, or drinking water in any treatment stage	Purging of organics from water using inert gas and trapping onto a sorbent. Thermal desorption of compounds onto GC. (EPA Method 502.1)	GC/electrolytic conductivity or GC/microcoulometric detector	0.01 µg/L	95 (n=18) at 0.40 µg/L	EPA 1988c
Water	Purge and trap (Standard Methods 6210D; equivalent to EPA Method 524)	GC/MS	0.02–0.2 µg/L	100 (12% RSD for n=7) at 0.5 µg/L (narrow bore capillary column)	APHA 1989a
Water	Purge and trap (Standard Methods 6230D; equivalent to EPA Method 502.2)	GC/PID/ELCD or microcoulometric detector	0.1–0.05 µg/L	99 at 10 µg/L; SD=6.8 µg/L	APHA 1989b
Municipal and industrial waste water	Purging of organics from water using inert gas and trapping onto a sorbent. Thermal desorption of compounds onto GC. (EPA Method 601)	GC/electrolytic conductivity or GC/micro-coulometric detector	30 ng/L (depending on interferences)	0.95 c + 0.19 where c=true value for concentration in µg/L	EPA 1984a

Table 6-2. Analytical Methods for Determining 1,1,2,2-Tetrachloroethane in Environmental Samples (continued)

Sample matrix	Sample preparation	Analytical method	Sample detection limit[a]	Percent Recovery	Reference
Groundwater and solid wastes	Purge and trap (EPA Method 8240)	GC/MS	Groundwater: 5 µg/L; soil/sediment: 5 µg/kg. Both values for fairly clean matrix; LODs much worse for complex wastes	0.93 c + 1.76 where c is concentration in µg/L	EPA 1986a
Waste water	Purge and trap onto Tenax/silica followed by thermal desorption	GC/MS (EPA Method 624)	6.9 µg/L	102 at 10–1,000 µg/L	EPA 1982a
Ground and surface water	Cryogenic trapping of analyte released into reduced pressure headspace (modification of vacuum distillation)	GC/ECD	1 ng/L	48	Comba and Kaiser 1983
Groundwater	Purge and trap onto Tenax/silica followed by thermal desorption	GC/MS (EPA-CLP Method)	5 µg/L	No data	EPA 1987a
Fish	Vacuum distillation and cryogenic trapping	HRGC/MS	No data	No data	Hiatt 1983
Various fatty and non-fatty foods and beverages	Extraction of clear beverages with isooctane. Homogenization of composited food with >70% fat or oil and direct dilution or melting followed by dilution with isooctane. Preparation of other foods with solid or pulpy consistency via extraction with 20% acetone - 5% NaCl in 25% phosphoric acid and isooctane. Isooctane analyzed directly by GC. Extracts from samples containing 21–70% fat had fat removed using Florisil.	GC/ECD or GC/ELCD	No data	Florisil treated: 38–122 (mean=80%, CV=23%) non-Florisil treated: 8–89 (mean=57%, CV=38%)	Daft 1989

Table 6-2. Analytical Methods for Determining 1,1,2,2-Tetrachloroethane in Environmental Samples (continued)

Sample matrix	Sample preparation	Analytical method	Sample detection limit[a]	Percent Recovery	Reference
Soil and sediment	Purging of sample suspension in water, adsorption of volatiled compounds onto Tenax/silica followed by thermal desorption	GC/MS	5 µg/kg	No data	EPA 1987a
Sediment	Purge and trap with collection of released compounds onto Porapak followed by desorption with methanol	HRGC/ECD	1 µg/kg	60–82	Amin and Narang 1985
Sediment	Extraction of sediment with methanol followed by transfer of an aliquot of methanol extract to water for purge and trap analysis.	GC/ECD/FID	0.05 µg/g (ppm)	84–86 (7% RSD)	Amaral et al. 1994
Sewage sludge	Extraction with pentane, addition of internal standard, filtration	GC/ECD	0.08 µg/L (wet)	111 (10.6% RSD)	Wilson et al. 1994
Liquid and solid waste	Dispersion of solid and viscous samples in a glycol followed by purge and trap using Tenax/silica/ charcoal and thermal desorption	GC/HECD (EPA Method 5030 and 8010)	0.3 µg/L (groundwater) 0.3 µg/kg (soil) 15 µg/L (liquid waste) 37.5 µg/kg (sludge or solid waste)	0.95 c + 0.19 where c is actual concentration	EPA 1982b, 1986b
Solid and liquid waste	Dispersion of solid and viscous samples in a glycol followed by purge and trap using Tenax/silica/ charcoal and thermal desorption	GC/HECD and PID in series	0.9 µg/L (water 1–5 mg/kg (soil)	93 at 6 µg/L (water)	Lopez-Avila et al. 1987

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

ECD = Electron Capture Detector; ELCD = Electrolytic Conductivity Detector; FID = Flame Ionization Detector; GC = Gas Chromatography; HECD = Hall Electrolytic Conductivity Detector; HRGC = High Resolution Gas Chromatography; MC = Microcoulometry; MS = Mass Spectrometry; PID = Photoionization Detector; RSD = relative standard deviation (coefficient of variation); SIM = selected ion monitoring

6. ANALYTICAL METHODS

desorption and analysis. The recoveries from the same type of tubes were very good when the tubes were stored frozen for up to 30 days after sample collection. Chemical transformation of 1,1,2,2-tetrachloroethane to trichloroethylene has been reported (NIOSH 1994) on certain types of charcoal sorbents. It is also important to note that water introduced to the GC after both cryogenic and sorbentbased collection methods can result in shifts in GC retention times and in the alteration of instrumental response in MS detection that results from pressure changes in the ion source during elution of the water.

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

The two routine quantification methods that provide the lowest detection limits are halogen-specific detection (e.g., Hall electrolytic conductivity detector) and MS. Since the compound has four chlorine atoms, electron capture detection (ECD) is also very sensitive for this compound. The advantages of halogen-specific detectors are they are not only very sensitive, but are also selective for halogencontaining compounds. The mass spectrometer, on the other hand, provides additional confirmation of the presence of a compound through the compound's characteristic fragmentation pattern, and this selectivity can be very desirable when the simultaneous quantification of many compounds is required.

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The inability of halogen-specific detectors to detect and quantify non-halogen compounds can be overcome by using other detectors (e.g., photoionization detector) in series (Driscoll et al. 1987; Lopez-Avila et al. 1987). Atomic emission detectors can provide signals from many elements within the molecule (C, H, and Cl for 1,1,2,2-tetrachloroethane) simultaneously (Ryan et al. 1990; Yieru et al. 1990a, 1990b). A detection limit of 10 pg 1,1,2,2-tetrachloroethane was reported using a helium discharge detector in conjunction with GC (Ryan et al. 1990).

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

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 1,1,2,2-tetrachloroethane 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 1,1,2,2-tetrachloroethane.

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

6. ANALYTICAL METHODS

6.3.1 Identification of Data Needs

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

In order to assess whether the current methods are adequate for the monitoring of background levels in humans, some calculations need to be done. If a Minimal Risk Level (MRL) to humans is assumed to be 0.6 mg/kg/day for an oral intermediate-duration exposure (Chapter 2), the dose to a 70-kg person will be 21 mg/day (7.3 µg/min) assuming 50% absorption. If 0.015% of the absorbed dose is excreted in urine per minute (Morgan et al. 1970) and a total urinary output of 1,400 ml/day is assumed, this results in a predicted concentration of approximately 2.3 ng/mL (2.3 ppt). At the chronic-duration MRL (0.04 mg/kg/day), the predicted concentration in urine, using the same assumptions as above, would be 0.15 mg/mL (0.15 ppb). The concentration is likely to be higher in blood and thus should be detectable by the method of Ashley et al. (1992), but this has not been shown. No LODs were reported for methods for the measurement of 1,1,2,2,-tetrachloroethane in urine. If present in blood, this compound should be detectable in breath, but no methods were reported. Thus, methods are needed for the measurement of 1,1,2,2-tetrachlorethane in biological matrices if detection of exposures at the MRLs are desired.

No metabolite or biomarker of 1,1,2,2-tetrachloroethane from human exposure specific to this compound has yet been identified (see Section 2.6). The changes in metabolite concentrations with time in human blood, urine, or other appropriate biological medium may be useful in estimating its rate of metabolism in humans. In some instances, a metabolite or a biomarker might be useful in

correlating the exposure doses to the human body burden but, as previously noted, the metabolites are not specific to 1,1,2,2-tetrachloroethane. Such studies on the levels of metabolites/biomarkers in human samples are not available for this compound, although metabolic products of this compound from animal and in vitro studies have been identified (see Chapter 2) and analytical methods for their quantification are available. The metabolites chloral hydrate, trichloroethanol, trichlorethanol glucuronide, and trichloroacetic acid have all been determined using variations of headspace analysis (Breimer et al. 1974; Christensen et al. 1988; Koppen et al. 1988). These compounds are metabolites of TCE that can be formed from 1,1,2,2-tetrachloroethane. Reported sensitivities were approximately 20 ng/mL (20 ppb). Assuming a greater abundance in urine of metabolites relative to parent compound, these methods might be adequate but this has not been demonstrated. Additional methods need to be validated or developed to detect metabolites of 1,1,2,2-tetrachloroethane after exposures at the MRLs.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. The occurrence of this compound in environmental media can be used to indicate possible exposure of humans to this compound through the inhalation of air and ingestion of drinking water and foods containing 1,1,2,2-tetrachloroethane. The MRL for intermediate-duration inhalation exposure is 0.4 ppm (see Section 2.5). Methods for the measurement of 1,1,2,2-tetrachloroethane in air at the ppt level and at least 85% accuracy are available (Atlas and Schauffler 1991; Class and Ballschmiter 1987; Singh et al. 1981). No new methods are needed for this compound in air. The MRL for oral exposure for intermediate duration is 0.6 mg/kg/day, and for chronic duration is 0.04 mg/kg/day (see Section 2.5). Methods for the measurement of 1,1,2,2-tetrachloroethane in drinking water are sensitive to sub-ppb (sub-μg/L) and ppt (ng/L) levels with 91-100% accuracy (APHA 1989a, 1989b; EPA 1986c, 1988d). No new methods are needed for drinking water. Very little information was found for 1,1,2,2-tetrachloroethane in food; additional detection methods are needed for foods.

Although the products of biotic and abiotic processes of this compound in the environment are adequately known, no systematic study is available that measures the concentrations of its reaction products in the environment. In instances where the product(s) of an environmental reaction is more toxic than the parent compound, it is important to know the level of the reaction products in the environment. It is known that 1,1,2,2-tetrachloroethane degrades under anaerobic conditions (e.g., in anaerobic landfills, leading to contamination of groundwater) and via hydrolysis to trichloroethylene

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(see Section 5.3.2, and Cooper et al. [1987] and Haag and Mill [1988]). Hallen et al. (1986) also reported isolating 1,1,2-trichloroethane, cis- 1,2-dichloroethylene, trans- 1,2-dichloroethylene, l,l-dichloroethylene, and vinyl chloride after 6 weeks of incubation of 1,1,2,2-tetrachloroethane in a simulated landfill. The analytical methods for the determination of the levels of these environmental reaction products of 1,1,2,2-tetrachloroethane are available. Drinking water would be expected to be the main route of oral exposure. All of these compounds can be measured in drinking water using EPA Method 502.2 (EPA 1988d). Method detection limits (μg/L) are stated to be 0.01 for trichloroethylene, not determined for 1,1,2-trichloroethane, 0.01 for cis-1,2-dichloroethylene, 0.05 for trans- 1,2-dichloroethylene, 0.07 for l,l-dichloroethylene, and 0.02 for vinyl chloride. Precisions were reported to be between 2 and 4% RSD. All of the stated degradation products except cis- and trans-1,2-dichloroethylene can be measured in soils and solid wastes using EPA method 8240 (EPA 1986a) with practical quantitation limits (PQLs) of approximately 5 μg/L in groundwater, 5 μg/kg in soils/sediments, and 0.5 mg/kg in wastes. All of the degradation products except cis- 1,2-dichloroethylene can be measured in municipal and industrial wastes with PQLs ranging from 0.02 μg/L for 1,1,2-trichloroethane to 0.18 μg/L for vinyl chloride. Assuming that the concentrations of these degradation products are much less than the concentration of 1,1,2,2-tetrachloroethane and knowing that the methods for the parent compound are sufficiently sensitive to measure background levels, no additional methods are needed at the present time.

6.3.2 Ongoing Studies

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

No other ongoing studies related to analytical methods were identified.

7. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding 1,1,2,2-tetrachloroethane in air, water, and other media are summarized in Table 7-1.

An intermediate-duration inhalation MRL of 0.4 ppm was derived. The MRL is based on a LOAEL of 130 ppm, 5 hours per day, 5 days per week for 15 weeks for hepatic effects in rats in a study by Truffert et al. (1977).

An intermediate-duration oral MRL of 0.6 mg/kg/day was derived. The MRL is based on a NOAEL of 56 mg/kg/day for reduced body weight gain in rats (NCI 1978). The LOAEL was 100 mg/kg/day.

A chronic-duration oral MRL of 0.04 mg/kg/day was derived. The MRL is based on a LOAEL of 43 mg/kg/day for respiratory effect in female rats given gavage doses of 1,1,2,2-tetrachloroethane in corn oil for 78 weeks in a study by NCI (1978).

The EPA reference dose for 1,1,2,2-tetrachloroethane is undergoing review by an EPA Workgroup. No EPA reference concentration exists for the compound.

1,1,2,2-Tetrachloroethane is on the list of chemicals appearing in "The Emergency Planning and Community Right-to-Know Act of 1986" (EPCRA) (EPA 1988). Section 313 of Title III of EPCRA requires owners and operators of certain facilities that manufacture, import, process, or otherwise use the chemicals on this list to report annually their release of those chemicals to any environmental media.

OSHA requires employers of workers who are occupationally exposed to 1,1,2,2-tetrachloroethane to institute engineering controls and work practices to reduce and maintain employee exposure at or below permissible exposure limits (PEL). The employer must use engineering and workpractice controls, if feasible, to reduce exposure to or below an 8-hour time-weighted average (TWA) of 1 ppm. Respirators must be provided and used during the time period necessary to install or implement feasible engineering and work practice controls (OSHA 1974).

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1,1,2,2-Tetrachloroethane is regulated by the Clean Water Effluent Guidelines as stated in Title 40, Section 400-475, of the Code of Federal Regulations. For each point source category, 1,1,2,2-tetrachloroethane may be regulated as one of a group of chemicals controlled as Total Toxic Organics, or may have a Zero Discharge Limitation. The point source categories for which 1,1,2,2-tetrachloroethane is controlled as a Total Toxic Organic include electroplating (EPA 1981), metal finishing (EPA 1983a), and coil coating (EPA 1982a). The point source category for which 1,1,2,2-tetrachloroethane has a Zero Discharge Limitation is steam electric power generation (EPA 1982b).

The Resource Conservation and Recovery Act (RCRA) identifies 1,1,2,2-tetrachloroethane as a hazardous waste when discarded as a commercial chemical product, off-spec species, container residue, or spill residue (EPA 1980a).

7. REGULATIONS AND ADVISORIES

7-1. Regulations and Guidelines Applicable to 1,1,2,2 Tetrachloroethane

Agency	Description	Information	Reference
INTERNATIONAL			
WHO		NA	
IARC	Cancer classification	3[a]	IARC 1987
NATIONAL			
Regulations:			
a. Air:			
EPA/OAR	Hazardous Air Pollutant	Yes	Clean Air Act Amendments Title III, Section 112(b) U.S. Congress 1990
	Performance Standards - Equipment Leaks in Synthetic Organic Chemical Manufacturing Industry	Yes	40 CFR 60.489 EPA 1983b
	Chemical Affected by Subpart NNN[a]	Yes	40 CFR 60.667 EPA 1990
OSHA	PEL (TWA)	5 ppm	29 CFR 1910.1000 OSHA 1974
		35 mg/m^3	
b. Water: EPA/OW	Ambient Water Quality Criterion	$1.7x10^{-1}$ µg/L	EPA 1980b 48 FR 79318 (11/28/80)
	Appendix D - NPDES Permit Application Testing Requirements (122.21)	Yes	40 CFR 122 EPA 1983a
	Form 2D	NA	40 CFR 122 EPA 1983a
	Identification of Test Procedures	Yes	40 CFR 136.3 EPA 1973
	Method 601 - Purgeable Halocarbons	Yes	40 CFR 136 EPA 1973
	Method 624 - Purgeables	Yes	40 CFR 136 EPA 1973
EPA-ODW	Special Monitoring for Inorganic and Organic Chemicals	Yes	40 CFR 141.40 EPA 1975
	Special Monitoring for Organic Chemicals	Yes	40 CFR 141.40 EPA 1975
c. Food: EPA/OPTS	Tolerance range for agriculture products	Yes	
d. Other:			
DOT	Hazard Classification ORM-A	Yes	49 CFR 172.101 DOT 1991a
	Labeling Requirements - Poison	Yes	49 CFR 172.101 and Subpart E DOT 1991a
EPA/OERR/ CEPP	Reportable Quantity	100 lb.	40 CFR 302 EPA 1985a

7. REGULATIONS AND ADVISORIES

7-1. Regulations and Guidelines Applicable to 1,1,2,2 Tetrachloroethane (continued)

Agency	Description	Information	Reference
NATIONAL (cont.)			
EPA/OSW	Appendix I - Constituents for Detection Monitoring in Municipal Solid Waste Landfills	Yes	40 CFR 258 EPA 1991
	Appendix II - List of Hazardous Inorganic and Organic Constituents	Provides 3 EPA test methods and Practical Quantitation Limits	40 CFR 258 EPA 1991
Guidelines:			
a. Air:			
ACGIH	Ceiling limit for Occupational Exposure (TLV-TWA)	1 ppm (skin)	ACGIH 1994
	TWA	6.9 mg/m^3	Sittig 1994
EPA	q_1* Cancer Slope Factor (inhalation exposure)	0.2 mg/kg/d	IRIS 1995
NIOSH	Recommended Exposure Limit for Occupational exposure (TWA)	1 ppm (air)	NIOSH 1992
	Immediately Dangerous to Life and Health	150 ppm	NIOSH 1992
b. Water: EPA/OW			
	q_1* cancer slope factor (oral exposure)	0.2 mg/kg/d	IRIS 1995
c. Other:			
EPA	Cancer classification	Group C[b]	IRIS 1995
NIOSH	Cancer classification	Potential occupational carcinogen	NIOSH 1992
NTP	Cancer classification	Positive (mice) Equivocal (male rats) Negative (female rats)	NTP 1995
STATE			
Regulations and Guidelines a. Air:			
	Acceptable Ambient Air Concentration Guidelines or Standards		NATICH 1992
AZ	1 hr. avg. time	3.3x10^1 µg/m^3 (4.81x10^{-3} ppm)	

7. REGULATIONS AND ADVISORIES

7-1. Regulations and Guidelines Applicable to 1,1,2,2 Tetrachloroethane (continued)

Agency	Description	Information	Reference
STATE (cont.)			
	24-hr. avg. time	8.8 $\mu g/m^3$ ($1.28x10^{-3}$ ppm)	
CT	8 hr. avg. time	$3.44x10^{1}$ $\mu g/m^3$ ($5x10^{-3}$ ppm)	
FL-FTLDLE	8 hr. avg. time	$7.0x10^{-2}$ $\mu g/m^3$ ($1.020x10^{-5}$ ppm)	
FL-PINELLA	8 hr. avg. time	$7.0x10^{1}$ $\mu g/m^3$ ($1x10^{-2}$ ppm)	
	24 hr. avg. time	$1.68x10^{1}$ $\mu g/m^3$ ($2.45x10^{-3}$ ppm)	
	Annual avg. time	$1.7x10^{-2}$ $\mu g/m^3$ ($2.48x10^{-6}$ ppm)	
FL-TAMPA	8 hr. avg. time	$7.0x10^{-2}$ mg/m^3 ($1.02x10^{-5}$ ppm)	
KS	Annual avg. time	$1.72x10^{-2}$ $\mu g/m^3$ ($2.51x10^{-6}$ ppm)	
KS-KC	1 yr. avg. time	$1.72x10^{-2}$ $\mu g/m^3$ ($2.51x10^{-6}$ ppm)	
LA	Annual avg. time	1.7 $\mu g/m^3$ ($2.48x10^{-4}$ ppm)	
MA	24 hr. avg. time	$1.87x10^{1}$ $\mu g/m^3$ ($2.72x10^{-3}$ ppm)	
	Annual avg. time	$2.0x10^{-2}$ $\mu g/m^3$ ($2.91x10^{-6}$ ppm)	

7-1. Regulations and Guidelines Applicable to 1,1,2,2 Tetrachloroethane (continued)

Agency	Description	Information	Reference
STATE (cont.)			
MI	Annual avg. time	2.0×10^{-2} µg/m^3 (2.91×10^{-6} ppm)	
NV	8 hr. avg. time	1.67×10^{-1} mg/m^3 (2.4×10^{-2} ppm)	
NY	1 yr. avg. time	2.33×10^{1} µg/m^3 (3.39×10^{-3} ppm)	
OK	24 hr. avg. time	6.8×10^{1} µg/m^3 (9.9×10^{-3} ppm)	
PA-PHIL.	1 yr. avg. time	1.68×10^{2} µg/m^3 (2.4×10^{-2} ppm)	
	(Not given)	2.4×10^{1} µg/m^3 (3.5×10^{-3} ppm)	
SC	24 hr. avg. time	3.5×10^{1} µg/m^3 (5.1×10^{-3} ppm)	
TX	30 min. avg. time	7.0×10^{1} µg/m^3 (1.0×10^{-2} ppm)	
	Annual avg. time	7.0 µg/m^3 (1.0×10^{-3} ppm)	
VA	24 hr. avg. time	1.2×10^{2} µg/m^3 (1.7×10^{-2} ppm)	
VT	Annual avg. time	1.7×10^{-2} µg/m^3 (2.5×10^{-6} ppm)	
WA-SWEST	24 hr. avg. time	2.33×10^{1} µg/m^3 (3.4×10^{-3} ppm)	

7. REGULATIONS AND ADVISORIES

7-1. Regulations and Guidelines Applicable to 1,1,2,2 Tetrachloroethane (continued)

Agency	Description	Information	Reference
STATE (cont.)			
b. Water:			
	Water Quality: Human Health		CELDs 1993
AL	Listed but no data		
AZ	Drinking water guideline	0.17 µg/L	
	Fish consumption	11.0 µg/L	
CA	Drinking water standard	1.0 µg/L	FSTRAC 1990
CT	Organism consumption only	11.0[a]	CELDs 1993
	Organism & water ingestion	0.17[a]	
DE	Freshwater fish ingestion	13.5 µg/L	
	Freshwater fish & water ingestion	0.17 µg/L	
	Marine/estuarine fish/sheelfish ingestion	1.9 µg/L	
FL	Domestic/Drinking water	1.0 µg/L	Sittig 1994
HI	Salfwater fish consumption	3.5 µg/L	CELDs 1993
IN	4-d avg.; outside of mixing zone	107µg/L	
KS	Drinking water guideline	1.7 µg/L	FSTRAC 1990
KY	Consumption of fish tissue	10.7 µg/L	CELDs 1993
	Water supply sources	0.17 µg/L	
LA	Drinking water supply	0.16 µg/L	
	Non-drinking water supply	1.80 µg/L	
MA	Domestic/Drinking water	2 µg/L	Sittig 1994
MI	Domestic/Drinking water	0.18 µg/L	Sittig 1994
MN	Drinking water guideline	2 µg/L	FSTRAC 1990
MO	Fish consumption	11 µg/L	CELDs 1993
	Drinking water supply	0.17 µg/L	
NJ	Domestic/Drinking water	2.0 µg/L	Sittig 1994
NY	Domestic/Drinking water	0-2.5 µg/L	
OR	Water & fish ingestion	0.17 µg/L	CELDs 1993
	Fish consumption only	10.7 µg/L	
RI	Drinking water guideline	2.0 µg/L	FSTRAC 1990
SD	Domestic water	0.17 µg/L	CELDs 1993
	All other uses	10.7 µg/L	CELDs 1993
TX	Domestic/Drinking water	4.26 µg/L	Sittig 1994

7-1. Regulations and Guidelines Applicable to 1,1,2,2 Tetrachloroethane (continued)

Agency	Description	Information	Reference
STATE (cont.)			
VT	Class A or B water	0.17[a]	CELDs 1993
	Class C water	10.7[a]	CELDs 1993
	Drinking water guideline	0.7 µg/L	FSTRAC 1990
WV	Public water supply	0.17 µg/L	CELDs 1993
WI	Public water supplies-warmwater sport fish communities	1.7 mg/L	
	Public water supplies-cold water communities	1.6 mg/L	
	Public water supplies-Great Lakes communities	1.6 mg/L	
	Non-public water supplies-warm water sport fish communities	64 mg/L	
	Non-public water supplies-cold water communities	22 mg/L	
	Non-public water fupplies-warm water forage and limited forage fish communities and limited aquatic life	350 mg/L	
	Water Quality: Aquatic Life		CELDs 1993
AZ	Acute-cold water fishery	4700 µg/L	
	Acute-warm water fishery	4700 µg/L	
	Effluent dominated water	4700 µg/L	
	Chronic-cold water fishery	3200 µg/L	
	Chronic- warm water fishery	3200 µg/L	
	Chronic-effluent dominated water	3200 µg/L	
HI	Acute- saltwater	3000 µg/L	
LA	Acute- freshwater	923 µg/L	
	Acute- marine water	902 µg/L	
	Chronic- freshwater	462 µg/L	
	Chronic- marine water	451[a]	
NJ	Freshwater	9320 µg/L	
OH	Exceptional, seasonal, and modified warm waters, outside mixing zone-max.	1000 µg/L	
	Exceptional, seasonal, and modified warm waters, outside mixing zone, 30-d avg.	360 µg/L	
	Exceptional, seasonal, and modified warm waters; human health, 30-d avg.	107 µg/L	
	Inside mixing zone - maximum	2000 µg/L	

7. REGULATIONS AND ADVISORIES

7-1. Regulations and Guidelines Applicable to 1,1,2,2 Tetrachloroethane (continued)

Agency	Description	Information	Reference
STATE (cont.)			
OH (cont.)	Cold water & limited resource warm water, outside mixing zone-max.	1000 µg/L	
	Cold water; outside mixing zone, 30-d avg.	360 µg/L	
OH	Cold water & limited resource warm water; outside mixing zone, human health, 30-d avg.	107 µg/L	
	Inside mixing zone, max.	2000 µg/L	
OR	Chronic-freshwater	2400 µg/L	
	Acute-marine	9020 µg/L	
WV	Warm water fishery stream	10.7 µg/L	
	Trout waters	10.7 µg/L	
	Small non-fishable streams	10.7 µg/L	
	Water Quality: Recreational Use		CELDs 1993
AZ	Full body contact	7 µg/L	
	Partial body contact	450 µg/L	
TN		110 µg/L	
	Groundwater Quality Standards		CELDs 1993
MO		0.17 µg/L	
	Groundwater Monitoring Parameters		CELDs 1993
CO		Yes	
IL		Yes	
LA		Yes	
MN		Yes	
WV		Yes	
WI		Yes	
NJ	NPDES Permits: Testing Requirements for Organic Toxic Pollutants	Yes	
SD	Surface water Discharge Permit Application Requirements: Testing Requirements for Organic Toxic Pollutant	Yes	
	Toxic Discharge		CELDs 1993
CA		1.2 mg/L (30-d avg.)	
WI		Yes	

7. REGULATIONS AND ADVISORIES

7-1. Regulations and Guidelines Applicable to 1,1,2,2 Tetrachloroethane (continued)

Agency	Description	Information	Reference
STATE (cont.)			
c. Other:			
	Hazardous Waste		CELDs 1993
IL		Yes	
LA		Yes	
MA		Yes (LDR)	
WV		Yes	
	Hazardous Waste Constituents		CELDs 1993
CO		Yes	
IL		Yes (App. H)	
LA		Yes	
MN		Yes	
ND		Yes (App. IV)	
WV		Yes (App. VIII)	
WI		Yes (App. IV)	

[a] Not classifiable as to its carcinogenicity to humans
[b] Animal carcinogen

ACGIH = American Conference of Governmental and Industrial Hygienists; CELDs = Computer-aided Environmental Legislative; Database; CEPP = Chemical Emergency Preparedness and Prevention; CPSC = Consumer Product Safety Commission; DOT = Department of Transportation; EPA = Environmental Protection Agency; EPCRA = Emergency Planning and Community Right-to-Know Act; FR = Federal Register; FSTRAC = Federal State Toxicology and Regulatory Alliance Committee; FTLDLE = Ft. Lauderdale; GC/MS = Gas Chromatography/Mass Spectrometry; IARC = International Agency for Research on Cancer; ID No = Identification Number; IRIS = Integrated Risk Information System; KC = Kansas City; LDR = Land Disposal Restrictions; mfd. = manufactured; LOAEL = Lowest Observed Adverse Effect Level; NA = Not available at the present time; NATICH = National Air Toxics Information Clearinghouse; NCI = National Cancer Institute; NIOSH = National Institute of Occupational Safety and Health; NOAEL = No Observed Adverse Effect Level; NPDES = National Pollutant Discharge Elimination System; NTP = National Toxicology Program; OAR = Office of Air and Radiation; OERR = Office of Emergency and Remedial Response; ORM = Other Regulated Materials; OSHA = Occupational Safety and Health Administration; OSW = Office of Solid Waste; OW = Office of Water; PEL = Permissible Exposure Level; Phil = Philadelphia; proc. = processed; RCRA = Resource Conservation and Recovery Act; SWEST = Southwest; TLV = Threshold Limit Value; TWA = Time Weighted Average; UN = United Nations; 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 (Koc) -- 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, or in mL/g or L/ng.

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 population and 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.

9. GLOSSARY

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 8hour shift.

9. GLOSSARY

q1* -- The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q1* 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 $\mu g/m^3$ 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 non-threshold 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 USC. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99-499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

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

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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.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name:	1,1,2,2-Tetrachloroethane
CAS number:	79-34-5
Date:	August 1996
Profile status:	Final
Route:	[X] Inhalation [] Chronic
Duration:	[ ] Acute [X] Intermediate [ ] Chronic
Key to figure:	14r
Species:	Rat

MRL: 0.4 [ ] mg/kg/day [X] ppm [ ] mg/m^3

Reference: Truffert K, Girard-Wallon C, Emmerich E, et al. 1977. Early experimental demonstration of the hepatotoxicity of some chlorinated solvents by the study of the synthesis of hepatic DNA. Arch Mal Prof Med Trav Secur Soc 38:261-263. (French)

Exuerimental design: Fifty-five female Sprague-Dawley rats were exposed to 130 ppm 1,1,2,2-tetrachloroethane for 5 hours per day, 5 days per week for 15 weeks. Liver, kidney, adrenal, genital, and lung pathologies were monitored and compared with controls.

Effects noted in studv and corresnonding doses: Increased liver weights, granulation and vacuolization in liver cells were noted at 130 ppm. Cellular changes regressed after 19 exposures and were no longer observed following the 39th exposure. No significant changes were noted in the other tissues monitored. Thus, 130 ppm was a minimal LOAEL for hepatic effects in rats, since the hepatic effects were reversible, were consistent with enzyme induction, and did not indicate a preneoplastic effect.

Dose endpoint used for MRL derivation: 130 ppm for hepatic effects

[ ] NOAEL [X] LOAEL

Uncertainty factors used in MRL derivation: 300

[ ] 1 [X] 3 [ ] 10 (for use of a minimal LOAEL)
[ ] 1 [ ] 3 [X] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [X] 10 (for human variability)

MRL = 130 ppm/300 = 0.4 ppm

Was a conversion factor used from ppm in food or water to a mg/bodv weight dose? No.
If so, explain: Not applicable

If an inhalation studv in animals. list conversion factors used in determining; human eauivalent dose: The LOAEL is for a gas:extrarespiratory effect in rats assuming periodicity was attained. Because the h:a lambda values are unknown for the experimental species (a) and humans (h), a default value of 1 is used for this ratio.

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Was a conversion used from intermittent to continuous exuosure? No. 1,1,2,2-Tetrachloroethane is absorbed quite well and rapidly eliminated. Thus, an adjustment is not needed from intermittent to continuous exposure.

Other additional studies or nertinent information that lend sunnort to this MRL: One of the most significant systemic effects of 1 ,1,2,2-tetrachloroethane is found on the liver. In humans exposed to 1,1,2,2-tetrachloroethane in the workplace, jaundice and enlarged liver were often reported (Coyer 1944; Horiguchi et al. 1964; Jeney et al. 1957; Koelsch 1915). However, exposure levels associated with liver effects in workers were not clearly defined. In another intermediate-duration inhalation study in rats, congestion and unspecified fatty degeneration of the liver were reported at 9,000 ppm, the lowest exposure level used (Horiuchi et al. 1962).

Agency Contact (Chemical Manager): Les Smith

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MINIMAL RISK LEVEL WORKSHEET

Chemical name	1,1,2,2-Tetrachloroethane
CAS number:	79-34-5
Date:	August 1996
Profile status:	Final
Route:	[ ] Inhalation [x] Oral
Duration:	[ ] Acute [X] Intermediate [ ] Chronic
Key to figure:	20r
Species:	Rat

MRL: 0.6 [X] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: NCI. 1978. National Cancer Institute. Bioassay of 1,1,2,2-Tetrachloroethane for possible carcinogenicity. NTIS PB277 4537GA, DHEW/PUB/NIH-78-827.

Experimental design: Groups of 5 male and 5 female Osborne-Mendel rats were administered 1,1,2,2-tetrachloroethane by gavage in corn oil 5 days per week for 6 weeks at doses of 56, 100, 178, 316, and 562 mg/kg/day, followed by a 2-week observation period.

Effects noted in study and corresnonding doses: A 24% reduction in body weight gain was seen at 100 mg/kg/day in the female rats, with no body weight effects noted at 56 mg/kg/day. In the male rats, a 38% reduction in body weight gain was noted at 178 mg/kg/day. No body weight effects were noted in the same study in mice. Thus, 56 mg/kg/day was a NOAEL for no body weight effects in female rats, and 100 mg/kg/day was a LOAEL.

Dose endnoint used for MRL derivation: 56 mg/kg/day for no body weight effects.

[X] NOAEL [ ]LOAEL

Uncertainty factors used in MRL derivation: 100

[] 1 []3 [] 10(foruseofaLOAEL)
[ ] 1 [ ] 3 [x] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [x] 10 (for human variability)

MRL = 56 mg/kg/day/100 = 0.6 mg/kg/day.

Was a conversion factor used from nnm in food or water to a mg/body weight dose? No.
If so, explain: No, the compound was administered by gavage.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:
Not applicable.

Was a conversion used from intermittent to continuous exnosure? No.

Other additional studies or pertinent information that lend support to this MRL: The only other available oral intermediate study is a 120-day oral gavage study in rats (Gohlke et al. 1977) in which several serious effects (e.g., necrosis and fatty degeneration of the liver, pyelonephritis, testicular atrophy) were noted in rats given 3.2 mg/kg/day. However, it was noted that rats in this study had been subjected to a 4-hour

period at 35 "C after dosing, which seriously compromised the reliability and validity of the results. In the NCI (1978) 78week study, groups of 50 male and 50 female Osborne-Mendel rats were treated by gavage with 1,1,2,2-tetrachloroethane in corn oil 5 days per week for 78 weeks, followed by a 32-week observation period. The doses were 62 or 108 mg/kg/day in males and 43 or 76 mg/kg/day in females. Male rats treated with 108 mg/kg/day were 20% lighter than vehicle controls at week 75. Body weights of female rats treated with 76 mg/kg/day appeared lower than controls throughout treatment; however by the end of the observation period there seemed to be no difference between groups.

Agency Contact (Chemical Manager): Les Smith

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name:	1,1,2,2-Tetrachloroethane
CAS number:	79-34-5
Date:	August 1996
Profile status:	Final
Route:	[ ] Inhalation [X] Oral
Duration:	[ ] Acute [ ] Intermediate [X] Chronic
Key to figure:	23r
Species:	Rat

MRL: 0.04 [X] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: NCI. 1978. National Cancer Institute. Bioassay of 1,1,2,2-Tetrachloroethane for possible carcinogenicity. NTIS PB277 4537GA, DHEW/PUB/NIH-78-827.

Exnerimental design: Groups of 50 male and 50 female Osborne-Mendel rats were administered 1,1,2,2-tetrachloroethane by gavage in corn oil 5 days per week for 78 weeks, followed by a 32-week observation period. Males received time-weighted average doses of 62 or 108 mg/kg/day, while females received time-weighted average doses of 43 or 76 mg/kg/day. Groups of 20 rats per sex were administered the vehicle alone or remained untreated. Body weight gain was monitored, and gross and histological examination of the major organs and tissues was performed.

Effects noted in study and corresnonding doses: Male rats exhibited labored respiration, wheezing, and nasal discharge at 62 mg/kg/day, while females showed the same symptoms at 43 mg/kg/day. Histological examination revealed no systemic effects in any organs examined, including the lungs and brain. In the same study, groups of mice had renal effects at 284 mg/kg/day, consisting of tubular nephrosis leading to death in males and hydronephrosis in females. No respiratory effects were noted in mice. Thus, 43 mg/kg/day was a LOAEL for respiratory effects in female rats.

Dose endnoint used for MRL derivation: 43 mg/kg/day for respiratory effects.

[ ] NOAEL [x] LOAEL

Uncertainty factors used in MRL derivation: 1,000

[ ] 1 [ ] 3 [x] 10 (for use of a LOAEL)
[ ] 1 [ ] 3 [x] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [x] 10 (for human variability)

MRL = 43 mg/kg/day/1,000 = 0.04 mg/kg/day

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.
If so, explain: No, the compound was administered by gavage.
If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? No.

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Other additional studies or pertinent information that lend support to this MRL: In the NCI (1978) study, groups of 50 male and 50 female $B6C3F_1$ mice were also treated by gavage with 1,1,2,2-tetrachloroethane in corn oil 5 days per week for 78 weeks, followed by a 12-week observation period. The doses were 142 or 284 mg/kg/day in both sexes. Groups of 20 mice per sex were administered the vehicle alone or remained untreated. Renal effects were found in both sexes of mice at 284 mg/kg/day and consisted of tubular nephrosis leading to death in males and hydronephrosis in females. No respiratory effects were found. No other chronic-duration oral studies were located. Reports from human autopsies following suicidal ingestion of 1,1,2,2-tetrachloroethane have revealed respiratory effects including congestion and edema of the lungs, and lung collapse (Hepple 1927; Mant 1953).

Agency Contact (Chemical Manager): Les Smith

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 (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of 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.

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(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 Fresuencv/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 IS), 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, 1 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.

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(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) Exnosure 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/m3 or ppm and oral exposure is reported in mgtkglday .

(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) CEL 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 Group's upper-bound estimatesof the slope of the cancer dose response curve at low dose levels (ql*).

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

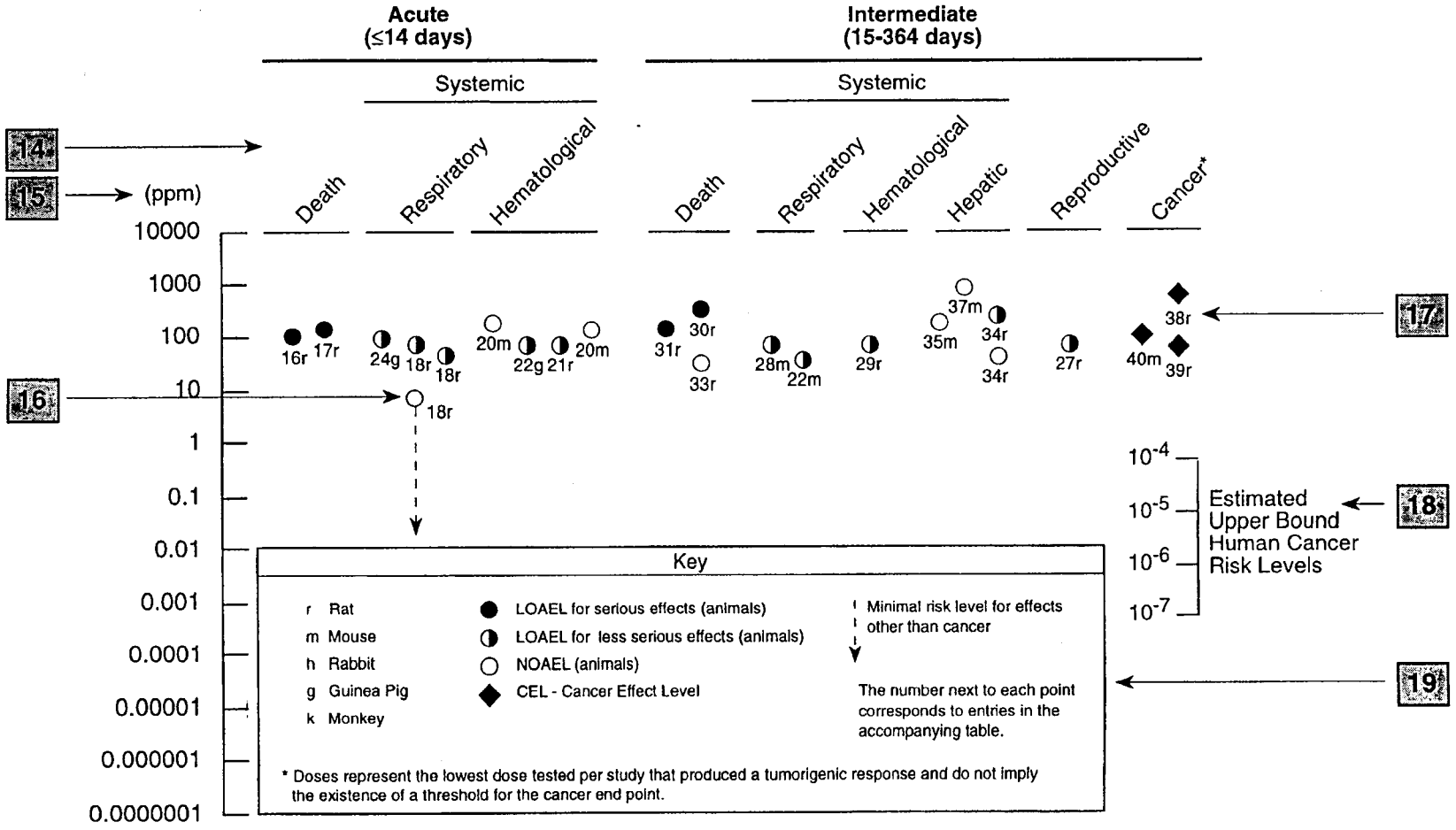
TABLE 2-1. Levels of Significant Exposure to [Chemical x] – Inhalation

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

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

[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5 x 10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

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



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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 (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. 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).

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To derive an MRL, 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 (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
C	Centigrade
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
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
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

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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
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mmhg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
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
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

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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
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	micron
μg	microgram

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