Toxicological Profile for 1,1,1-Trichloroethane

March 2024

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

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DISCLAIMER

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FOREWORD

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

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

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a relevance to public health discussion which would allow a public health professional to make a real-time determination of whether the presence of a particular substance in the environment poses a potential threat to human health. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to the protection of public health are identified by ATSDR.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance due to associated acute-, intermediate-, and chronic-duration exposures;

(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, intermediate, and chronic health effects; and

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

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

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

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VERSION HISTORY

Date	Description
March 2024	Final toxicological profile released
January 2023	Draft for public comment toxicological profile released
July 2006	Final toxicological profile released
August 1995	Final toxicological profile released
December 1990	Final toxicological profile released

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ATSDR scientists review peer reviewers' comments and determine whether changes will be made to the profile based on comments. The peer reviewers' comments and responses to these comments are part of the administrative record for this compound.

The listing of peer reviewers should not be understood to imply their approval of the profile's final content. The responsibility for the content of this profile lies with ATSDR.

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CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

1,1,1-Trichloroethane is a synthetic chemical that does not occur naturally in the environment. It is introduced into the environment by human activity. 1,1,1-Trichloroethane also is known as methyl chloroform, methyltrichloromethane, trichloromethylmethane, and α-trichloromethane. Its registered trade names are Tri-Ethane™, chloroethene NU®, and Aerothene TT®. It is a colorless liquid with a sweet, sharp odor. 1,1,1-Trichloroethane dissolves slightly in water. The liquid evaporates quickly and becomes a vapor. Most people begin to smell 1,1,1-trichloroethane in the air when its levels reach 120–500 (ppm). If the chemical makes up 7.5–12.5% (7,000–125,000 ppm) of the air, it can burn easily when it contacts a spark or flame (NIOSH 2019). A poisonous gas known as phosgene can be produced when 1,1,1-trichloroethane is heated to decomposition or during welding if 1,1,1-trichloroethane is used to clean the metal (Reid and Muianga 2012). 1,1,1-Trichloroethane also can be found in soil and water, particularly at hazardous waste sites. Because of its tendency to evaporate easily, the vapor form is most commonly found in the environment.

1,1,1-Trichloroethane had many industrial and household uses. It was often used as a solvent to dissolve other substances, such as glues and paints. In industry, it was widely used to remove oil or grease from manufactured parts. In the home, it used to be an ingredient of products such as spot cleaners, glues, and aerosol sprays. The production of 1,1,1-trichloroethane was banned for domestic use in the United States after January 1, 2002 by the U.S. Environmental Protection Agency (EPA) because it affects the ozone layer. However, until 2005, limited amounts were still allowed to be produced for essential purposes, and until 2012, production of 1,1,1-trichloroethane was allowed for export. U.S. production of 1,1,1-trichloroethane was intended to be incrementally cut as per Section 604 of the Clean Air Act and Montreal Protocol (Kapp 2014). 1,1,1-Trichloroethane was slated to be phased out by January 2002 and production stopped by 2012 as a result of ozone depletion agreements from the Montreal Protocol (Kapp 2014). While the Montreal Protocol did not stop the production of 1,1,1-trichloroethane, it did reduce the production, thus resulting in a steady decline in ambient levels. Some production of 1,1,1-trichloroethane does continue (CDR 2020), and the waste management and/or disposal agencies continue processing and destroying 1,1,1-trichloroethane. Some U.S. facilities continue to report quantities of 1,1,1-trichloroethane to EPA databases such as the Toxics Release Inventory (TRI) and Chemical Data Reporting (CDR); most of these are predominantly hazardous waste management and/or disposal facilities that process and destroy large volumes of 1,1,1-trichloroethane.

Health effects are observed when there is an exposure to large amounts of 1,1,1-trichloroethane. 1,1,1-Trichloroethane is found in air samples taken from all over the world. In the United States, levels in outdoor air between 2003 and 2004 averaged around 0.2 µg/m^3 (0.04 ppb) of 1,1,1-trichloroethane, with a maximum concentration of around 0.9 µg/m^3 (0.2 ppb) (Brenner 2010). Levels in indoor air averaged around 0.2 µg/m^3 (0.04 ppb) of 1,1,1-trichloroethane, with a maximum concentration also around 0.2 µg/m^3 (0.04 ppb) (Brenner 2010). More recent ambient air measurements taken in 2020 are considerably lower, with a median concentration of 0 and a maximum concentration of around 0.3 µg/m^3 (0.06 ppb) (EPA 2022a). 1,1,1-Trichloroethane has also been found in water samples from wells near waste disposal sites.

Common consumer products that contained 1,1,1-trichloroethane included glues, household cleaners, and aerosol sprays. In the workplace, exposure to 1,1,1-trichloroethane could occur while using some metal degreasing agents, paints, glues, and cleaning products, especially from inhalation of vapors or dermal exposure to liquids containing 1,1,1-trichloroethane. High levels of exposure have occurred when 1,1,1-trichloroethane vapors were deliberately inhaled, as in glue-sniffing or solvent abuse. However, as 1,1,1-trichloroethane has been phased out of production in the United States, the current exposure risk from consumer products and in workplaces is likely minimal.

1.2 SUMMARY OF HEALTH EFFECTS

The health effects of 1,1,1-trichloroethane have been evaluated in epidemiological studies, controlled human trials, and experimental animal studies. Toxicity studies on 1,1,1-trichloroethane have evaluated a variety of endpoints, primarily neurological, hepatic, body weight, cardiovascular, and developmental. The genotoxicity of 1,1,1-trichloroethane has also been tested on a variety of species test systems.

As displayed in Figures 1-1, 1-2, and 1-3, the most sensitive endpoints for 1,1,1-trichloroethane toxicity appear to be neurological and hepatic. A systematic review was conducted on these endpoints. Weight-of-evidence conclusions are defined in Appendix C. The review resulted in the following hazard identification[1] conclusions:

- Neurological effects are a known health effect with inhalation exposure.
- Hepatic effects are a presumed health effect with inhalation exposure.

[1]For additional details on the definitions on the hazard identification categories, the reader is referred to Appendix C.

Figure 1-1. Health Effects Found in Humans Following Inhalation Exposure to 1,1,1-Trichloroethane

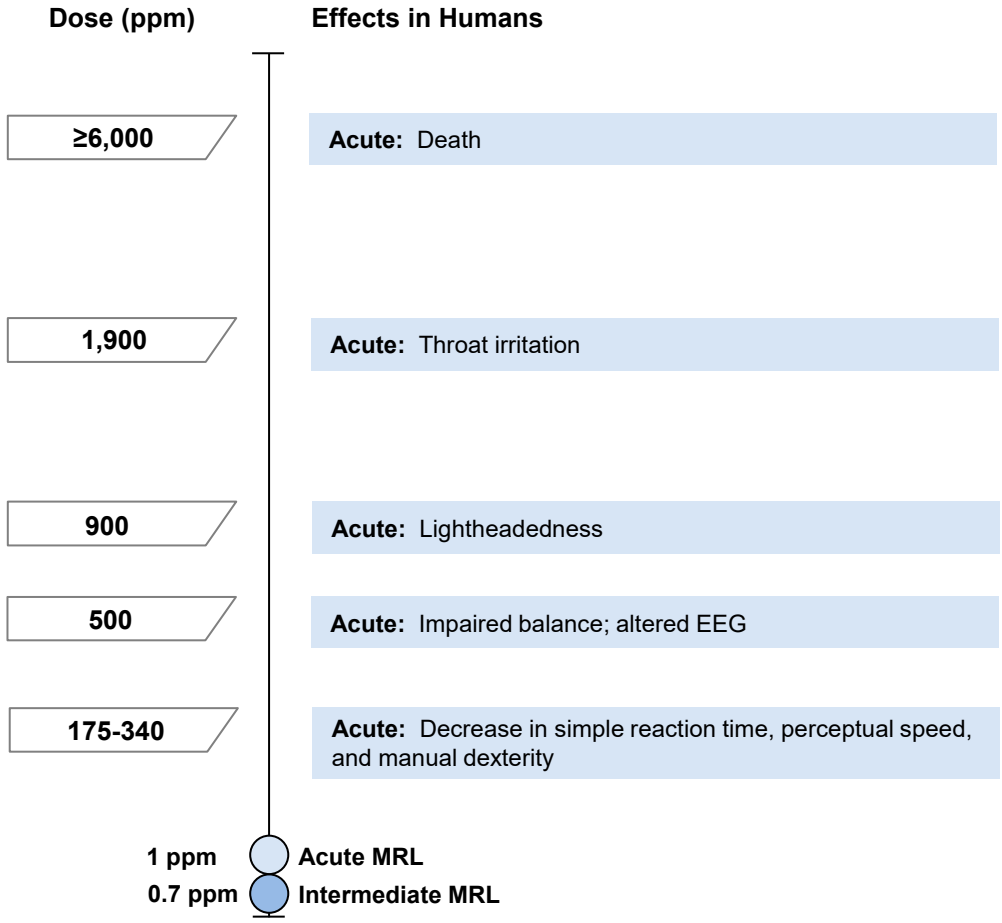


Figure 1-2. Health Effects Found in Animals Following Inhalation Exposure to 1,1,1-Trichloroethane

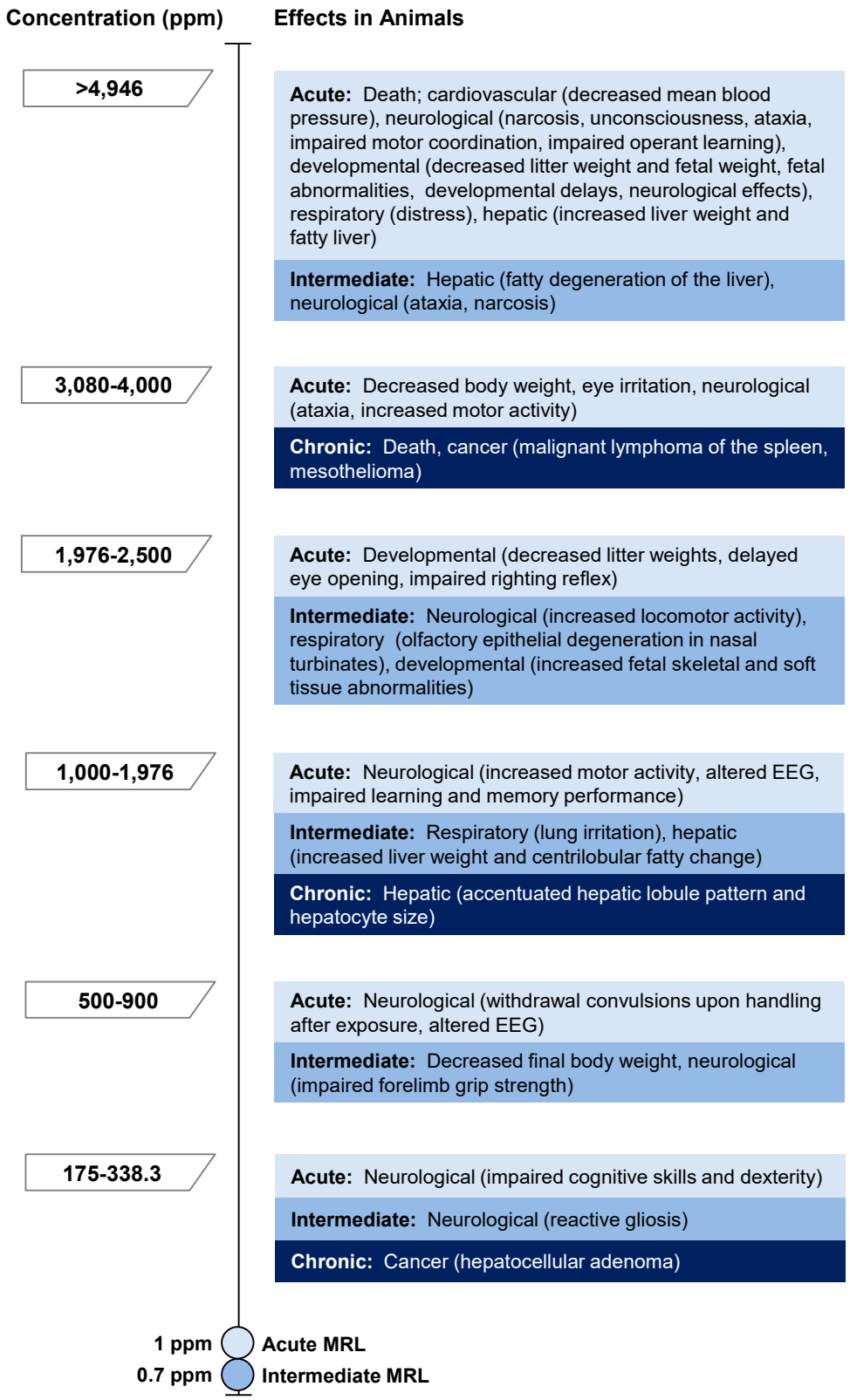
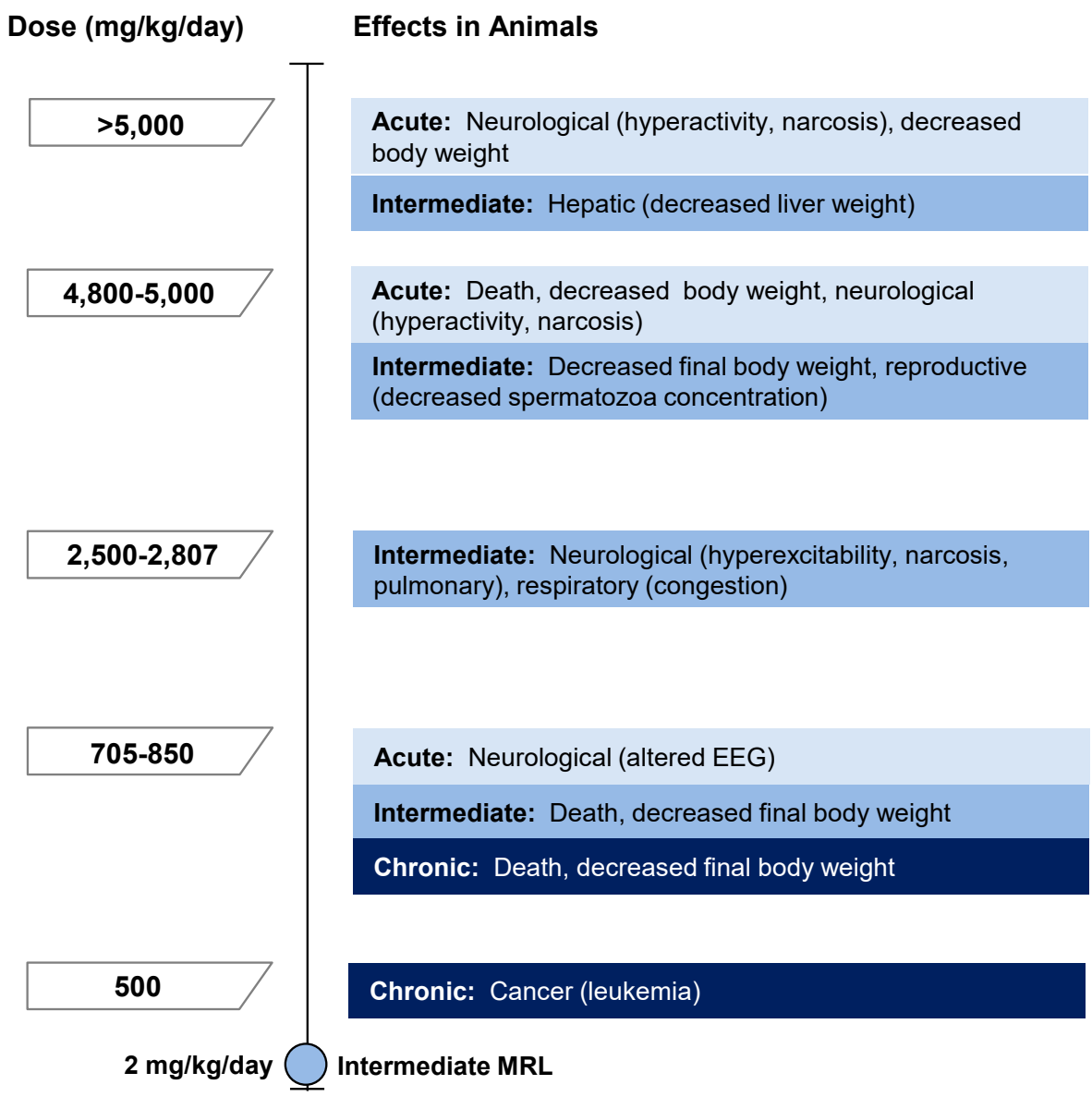


Figure 1-3. Health Effects Found in Animals Following Oral Exposure to 1,1,1-Trichloroethane



Neurological Effects. Inhalation studies in laboratory animals and humans strongly support neurological effects as one of two most sensitive endpoints following exposure to 1,1,1-trichloroethane. Observed health effects in controlled human exposure studies include impaired cognitive skills and manual dexterity, as well as disturbances of equilibrium and coordination (Gamberale and Hultengren 1973; Mackay et al. 1987; Muttray et al. 2000; Stewart et al. 1961). The principal neurological effects observed in animals exposed to 1,1,1-trichloroethane are signs of central nervous system depression, such as impaired performance in behavioral tests, ataxia, and unconsciousness, and are similar to those seen in

humans (Adams et al. 1950; Balster et al. 1982; Calhoun et al. 1981; Evans and Balster 1993; Geller et al. 1982; George et al. 1989; Jones et al. 1996; Mullin and Krivanek 1982; Torkelson et al. 1958). In addition, neurochemical (Hougaard et al. 1984; Rosengren et al. 1985; You and Dallas 2000), behavioral (Balster et al. 1982; Bowen and Balster 1996, 1998, 2006; Bowen et al. 1996a, 1996b; Kjellstrand et al. 1985b; Mullin and Krivanek 1982; Mattsson et al. 1993), and physiological (Evans and Balster 1993) changes have also been observed.

Hepatic Effects. Studies in laboratory animals support hepatic toxicity as another sensitive endpoint following inhalation exposure to 1,1,1-trichloroethane. Although no evidence of liver effects was noted in controlled exposure studies in humans, data from case reports of individuals exposed to high 1,1,1-trichloroethane concentrations suggest that the chemical may produce hepatic effects in humans, including changes in liver enzymes and progressive liver disease (Cohen and Frank 1994; Halevy et al. 1980; Hodgson et al. 1989). Consistent effects were observed in animal studies, which suggest 1,1,1-trichloroethane produces hepatic effects after inhalation exposure. The liver effects include increased liver weight, fatty changes in the liver, and swelling of hepatocytes (Adams et al. 1950; Fuller et al. 1970; Koizumi et al. 1983; MacEwen and Vernot 1974; McNutt et al. 1975; Quast et al. 1988; Toftgard et al. 1981; Torkelson et al. 1958).

1.3 MINIMAL RISK LEVELS (MRLS)

Minimal risk levels (MRLs) for inhalation and oral exposures to 1,1,1-trichloroethane were derived. Figures 1-4 and 1-5 summarize sensitive targets of 1,1,1-trichloroethane for inhalation and oral exposures, respectively. As shown in Table 1-1 and discussed in greater detail in Appendix A, the inhalation database was considered adequate for derivation of acute- and intermediate-duration MRLs for 1,1,1-trichloroethane. The oral database was considered adequate for derivation of an intermediate-duration MRL.

As illustrated in Figure 1-4, neurological and hepatic effects appear to be the most sensitive targets of inhaled 1,1,1-trichloroethane. As shown in Figure 1-5, the most sensitive targets for oral exposure are neurological for acute-duration exposure, body weight for intermediate-duration exposure, and body weight and cancer for chronic-duration exposure.

Figure 1-4. Summary of Sensitive Targets of 1,1,1-Trichloroethane – Inhalation

Available data indicate that the neurological and hepatic endpoints are the most sensitive targets of 1,1,1-trichloroethane following inhalation exposure.

Number in triangles and circles are the lowest LOAELs among health effects in humans and animals, respectively.

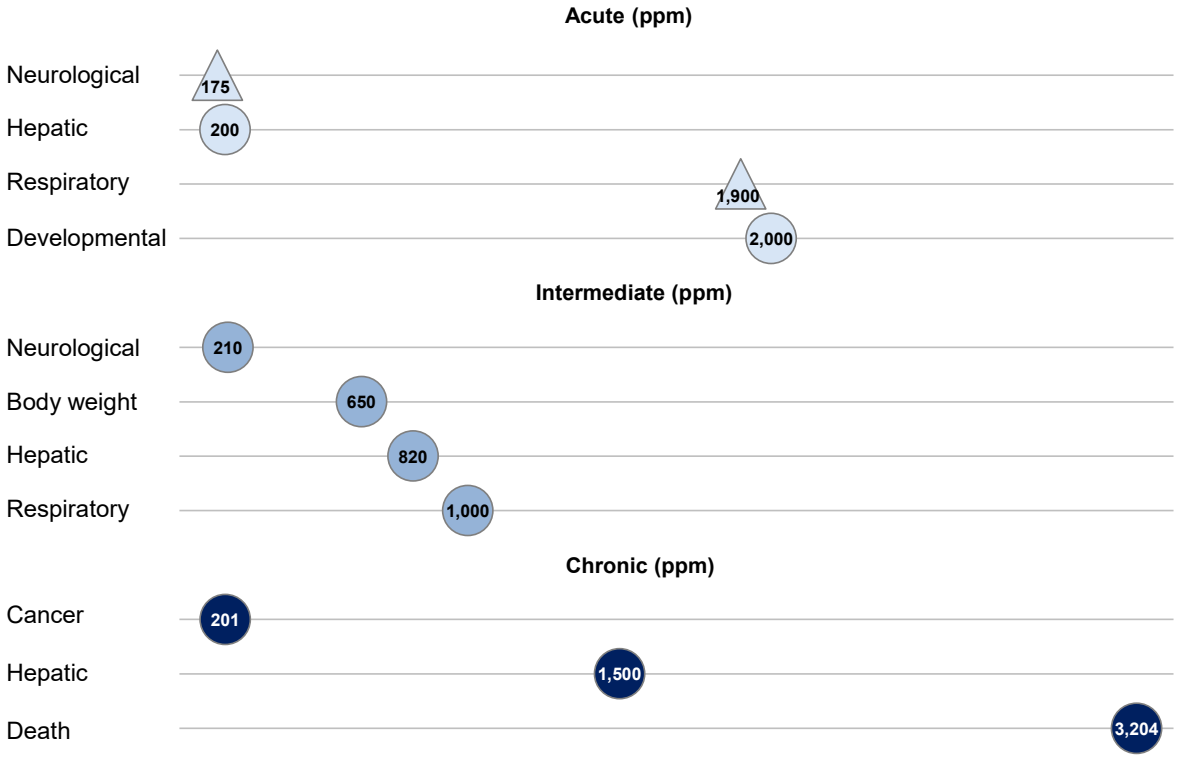


Figure 1-5. Summary of Sensitive Targets of 1,1,1-Trichloroethane – Oral

Available data indicate that the neurological and hepatic endpoints are the most sensitive targets of 1,1,1-trichloroethane following oral exposure.

Numbers in circles are the lowest LOAELs among health effects in animals.

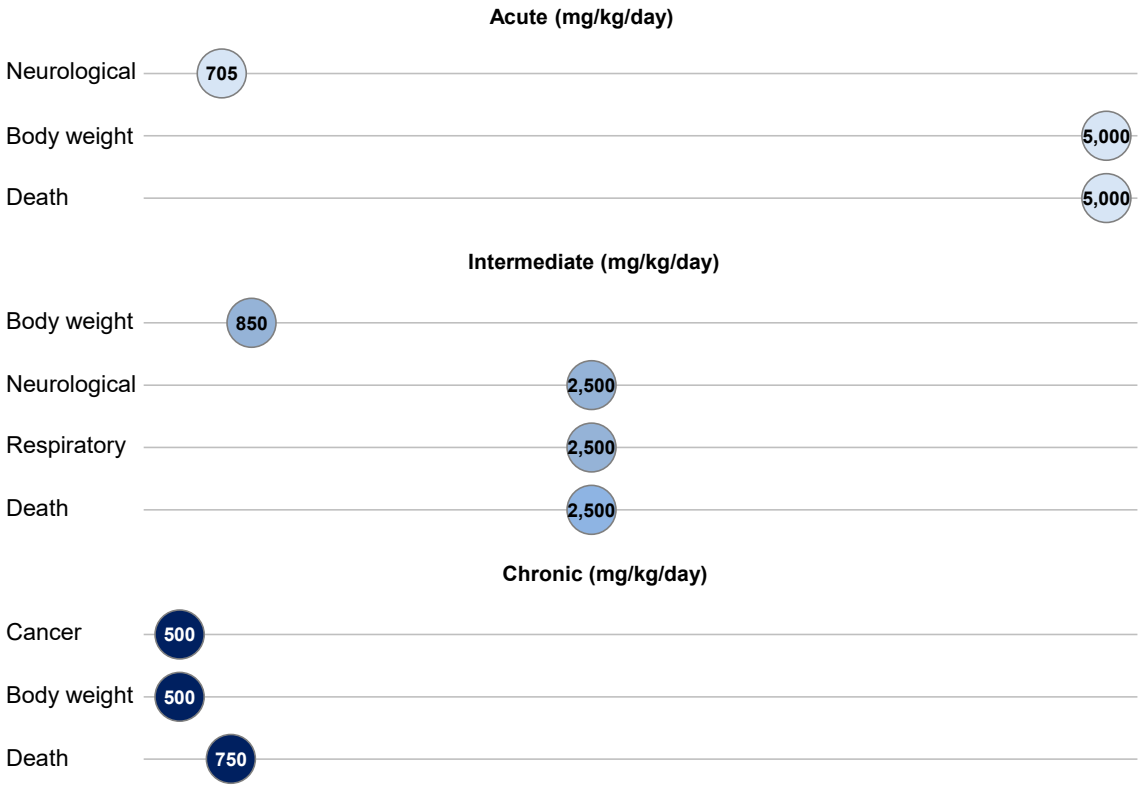


Table 1-1. Minimal Risk Levels (MRLs) for 1,1,1-Trichloroethane[a]

Exposure route	Exposure duration	MRL	Critical effect	POD type	POD value	Uncertainty/ modifying factor	Reference
Inhalation	Acute	**1 ppm** (6 mg/m^3)	Impaired performance in measures of cognitive skills in humans	$LOAEL_{ADJ}$	119 ppm	UF: 100	Mackay et al. 1987
	Intermediate	**0.7 ppm** (4 mg/m^3)	Reactive gliosis measured by increased GFAP in gerbils	NOAEL	70 ppm	UF: 100	Rosengren et al. 1985
	Chronic	None	–	–	–	–	–
Oral	Acute	None	–	–	–	–	–
	Intermediate	**2 mg/kg/day**	Decreased final body weight in mice	$BMDL_{10}$	208 mg/kg/day	UF: 100	NTP 2000
	Chronic	None	–	–	–	–	–

[a]See Appendix A for additional information.

ADJ = adjusted for intermittent exposure; $BMDL_{10}$ = benchmark dose lower confidence limit 10%; GFAP = glial fibrillary acid protein; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; UF = uncertainty factor

CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of 1,1,1-trichloroethane. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health. When available, mechanisms of action are discussed along with the health effects data; toxicokinetic mechanistic data are discussed in Section 3.1.

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

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 by health effect. These data are discussed in terms of route of exposure (inhalation, oral, and dermal) and three exposure periods: acute (≤14 days), intermediate (15–364 days), and chronic (≥365 days).

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figure 2-1 provides an overview of the database of studies in humans or experimental animals included in this chapter of the profile. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to 1,1,1-trichloroethane, but may not be inclusive of the entire body of literature. A systematic review of the scientific evidence of the health effects associated with exposure to 1,1,1-trichloroethane was also conducted; the results of this review are presented in Appendix C.

Summaries of the human observational studies are presented in Table 2-1. Animal inhalation studies are presented in Table 2-2 and Figure 2-2, animal oral studies are presented in Table 2-3 and Figure 2-3, and animal dermal studies are presented in Table 2-4.

Levels of significant exposure (LSEs) for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. Effects have been classified into “less serious LOAELs” or “serious LOAELs (SLOAELs).” "Serious" effects (SLOAELs) are those that evoke failure in a biological system and can lead to morbidity or

mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an endpoint 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 endpoints. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

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

The health effects of 1,1,1-trichloroethane have been evaluated in epidemiological studies, human controlled trials, and experimental animal studies. As illustrated in Figure 2-1, most of the health effects data come from inhalation exposure studies in animals. Animal data are available for each health effect category and exposure duration category. Much of the data for 1,1,1-trichloroethane comes from toxicity studies that evaluated numerous endpoints. The most reported effects on systems from the literature include body weight, neurological, hepatic, and respiratory effects of 1,1,1-trichloroethane. A number of cohort studies mainly summarized the impact that 1,1,1-trichloroethane had on the nervous and reproductive systems and the potential association with various cancers.

As outlined in Chapter 1, the most sensitive effects from 1,1,1-trichloroethane exposure appear to be neurological and hepatic. A systematic review was conducted on these endpoints. The information in those human and animal studies indicates the following potential targets of 1,1,1-trichloroethane toxicity.

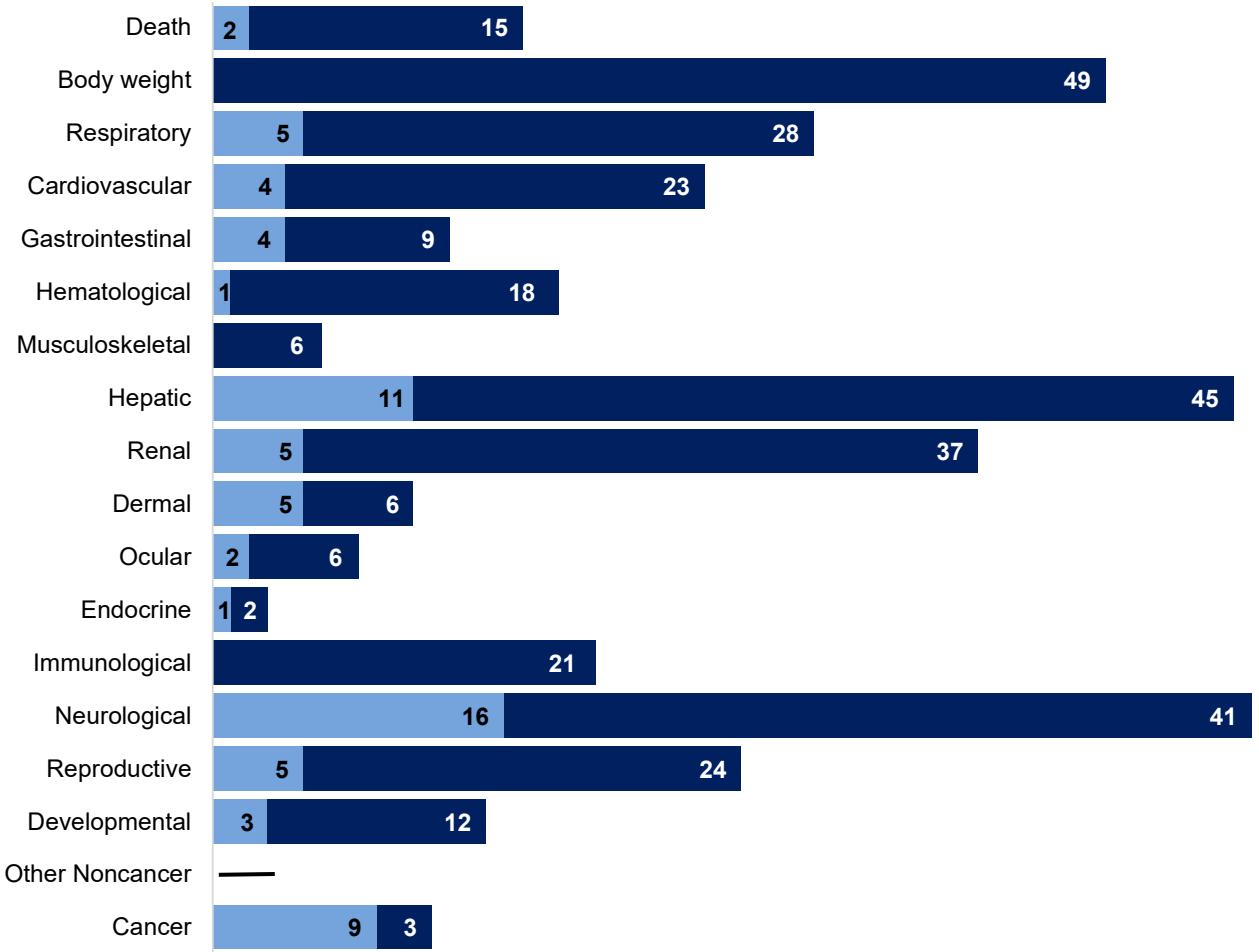
- **Neurological Endpoints.** Neurological effects are a known health effect associated with 1,1,1-trichloroethane exposure via inhalation based on the systematic review. Controlled human exposure studies clearly indicate neurological effects associated with 1,1,1-trichloroethane exposure (e.g., Gamberale and Hultengren 1973; Mackay et al. 1987; Muttray et al. 2000; Stewart et al. 1961; Torkelson et al. 1958). Animal studies provide strong supporting evidence from acute- and intermediate-duration assessments. The nervous system impacts ranging from observable changes in outcomes such as ataxia and behavior to neurophysiological changes such

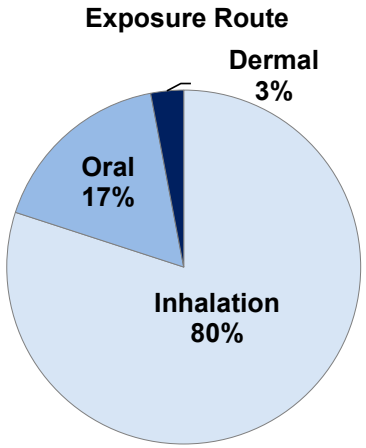
as changes in electroencephalogram or increased brain weight (Balster et al. 1982; Bowen and Balster 1996, 1998; Hougaard et al. 1984; Kjellstrand et al. 1985b; Mullin and Krivanek 1982; Torkelson et al. 1958).

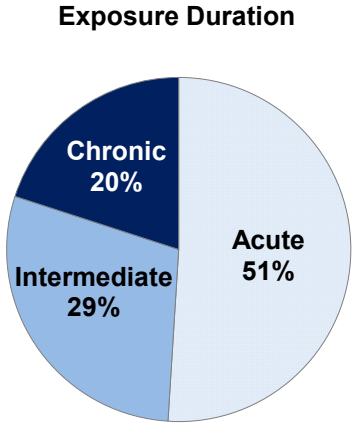
- **Hepatic Endpoints.** Hepatic effects are a presumed health effect for humans exposed to 1,1,1-trichloroethane via inhalation based on evidence in animals following acute-, intermediate-, and chronic-duration exposure. Although no evidence of liver effects was noted in controlled exposure studies in humans, data from case reports of overexposed humans suggest that the chemical may produce hepatic effects in humans exposed to high levels (Cohen and Frank 1994; Halevy et al. 1980; Hodgson et al. 1989). Consistent effects were observed in animal studies, which suggest that 1,1,1-trichloroethane produces hepatic effects after inhalation exposure. The liver effects include changes in relative liver weight, fatty changes in the liver, and swelling of hepatocytes (Adams et al. 1950; Koizumi et al. 1983; MacEwen and Vernot 1974; McNutt et al. 1975; Quast et al. 1988; Toftgard et al. 1981; Torkelson et al. 1958).

Figure 2-1. Overview of the Number of Studies Examining 1,1,1-Trichloroethane Health Effects*

Most studies examined the potential neurological, hepatic, body weight, renal, and respiratory effects of 1,1,1-trichloroethane
Fewer studies evaluated health effects in humans than animals (counts represent studies examining endpoint)







*Includes studies discussed in Chapter 2. A total of 163 studies (including those finding no effect) have examined toxicity. Studies may have examined more than one endpoint for health effects.

Table 2-1. Occupational Inhalation Exposures to 1,1,1-Trichloroethane and Health Outcome Associations

Reference, study type, and study population	Exposure	Outcomes
Cancer		
Rohr Indus Inc. 1986, 1987 Case-control study of esophageal and stomach cancer (22 cases and 88 controls) in Rohr factory workers, 1958–1982	Classified as ever versus never exposed.	Esophageal or stomach cancer: ↔
Spirtas et al. 1991 Retrospective cohort study of cancer mortality in aircraft maintenance facility workers (n=14,457), Hill Air Force Base, Utah,1952–1982	NR	All cancer mortality: ↓ NHL mortality: ↔ MM mortality: ↑ Leukemia: ↔
Heineman et al. 1994 Case-control study of astrocytic brain cancer (300 cases and 320 controls) in Louisiana, New Jersey, and Pennsylvania, 1978–1981	Qualitative exposure classified as no exposure, low, medium, and high	Astrocytic brain cancer: ↔
Anttila et al. 1995 Retrospective cohort study of cancer incidence in Finnish workers (n=4,004), 1967–2002	Urinary 1,1,1-trichloroethane Men: 6.4 mg/L Women: 8.4 mg/L	All cancer: ↑ Stomach cancer: ↑ nervous system cancer: ↑ cervical cancer: ↑ Prostate cancer: Leukemia: ↔ NHL: ↑ MM: ↔
Infante-Rivard et al. 2005 Case-control study of childhood leukemia following maternal exposure (790 cases and 790 controls) in Canada, 1980–2000	Maternal exposure classified as no exposure and any exposure	Acute lymphoblastic leukemia in children: ↔

Table 2-1. Occupational Inhalation Exposures to 1,1,1-Trichloroethane and Health Outcome Associations

Reference, study type, and study population	Exposure	Outcomes
Gold et al. 2011 Case-control study of multiple myeloma (180 cases and 481 controls) in Washington and Michigan, 2000–2002	Classified as ever exposed	MM: ↑
Neta et al. 2012 Case-control study of brain tumors (489 glioma cases, 197 meningioma cases, and 799 controls) in Boston, 1994–1998	Classified as unexposed, possible exposure, and probably exposure	Glioma: ↔ Meningioma: ↔
McLean et al. 2014 Case-control study of brain tumors (1,906 cases and 5,565 controls) in Australia, Canada, France, Germany, Israel, New Zealand, and the United Kingdom, 2000–2004	Mean cumulative exposure: Cases: 188 ppm Controls: 458 ppm	Meningioma: ↔
Purdue et al. 2017 Case-control study of kidney cancer (1,217 cases and 1,235 controls) in Michigan and Illinois, 2002–2007	Stratified by probability of exposure: 0, <10, 10–49, 50–89, and ≥90%	Kidney cancer: ↔ (≥90% probability of exposure)
Talibov et al. 2017 Case-control study of adult chronic lymphocytic leukemia (20,615 cases and 103,075 controls) in Finland, Iceland, Norway, and Sweden, 1961–2005	Cumulative exposure stratified in tertiles (T) T1: ≤5.6 ppm-years T2: 5.6–12.9 ppm-years T3: >12.9 ppm-years	Chronic lymphocytic leukemia: ↔
Cardiovascular		
Kramer et al. 1978 Cross-sectional matched-pair study of health effects in workers from two factories (151 matched pairs) in North Carolina, 1975	TWA exposure levels stratified by quintile: Q1: <15 ppm Q2: 15–49 ppm Q3: 50–99 ppm Q4: 100–149 ppm Q5: 150–249 ppm	Blood pressure: ↔ Heart rate: ↔ P-wave duration: ↑

Table 2-1. Occupational Inhalation Exposures to 1,1,1-Trichloroethane and Health Outcome Associations

Reference, study type, and study population	Exposure	Outcomes
Hepatic		
Kramer et al. 1978 Cross-sectional matched-pair study of health effects in workers from two factories (151 matched pairs) in North Carolina, 1975	TWA exposure levels stratified by quintile: Q1: <15 ppm Q2: 15–49 ppm Q3: 50–99 ppm Q4: 100–149 ppm Q5: 150–249 ppm	Alkaline phosphatase: ↔ Bilirubin: ↔ gamma-Glutamyl transferase: ↑
Neurological		
Maroni et al. 1977 Cross-sectional study of neurological effects in female factory workers (n=29), circa 1977	Range of 1,1,1-trichloroethane concentrations in work areas: 200–990 ppm	Peripheral neuropathy: ↔ Superficial sensory response: ↔ Deep sensory response: ↔ Motor conduction (ulnar and peroneal nerves): ↔ Psychological test battery: ↔
Renal		
Radican et al. 2006 Retrospective cohort study of ESRD in U.S. aircraft workers (n=14,455), Hill Air Force Base, 1973–2002 (Utah)	Stratified in tertiles by years of exposure: T1: <2.5 years T2: 2.5–10 years T3: >10 years	ESRD: ↑ (T3)
Reproductive		
Taskinen et al. 1989 Case-control study of adverse pregnancy outcomes in partners of Finnish factory workers (103 cases, 182 controls), 1965–1983	Paternal exposure classified as unexposed, potentially exposed, and exposure likely	Spontaneous abortion: ↔
Lindbohm et al. 1990 Case-control study of spontaneous abortions (73 cases and 167 controls) in exposed female workers in Finland, 1973–1983	Classified as no, low, and high exposure	Spontaneous abortions: ↔

Table 2-1. Occupational Inhalation Exposures to 1,1,1-Trichloroethane and Health Outcome Associations

Reference, study type, and study population	Exposure	Outcomes
Sallmen et al. 1998 Cohort study of fertility in male Finnish factory workers (n=282), 1973–1983	Paternal exposure classified as none, low/intermediate, and high/frequent	Number of menstrual cycles to pregnancy: ↔

↑ = increase; ↓ = decrease; ↔ = no change; ESRD = end-stage renal disease; MM = multiple myeloma; NHL = Non-Hodgkin's lymphoma; NR = exposure not reported; Q = quintile; T = tertile; TWA = time-weighted average

Table 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
Gamberale and Hultengren 1973									
1	Human 12 M	1 day 4 times/day 30 minutes/ exposure	0, 239.2, 338.3, 451.2, 565.8	CS, NX	Cardio	565.8			
					Neuro	239.2	338.3		Impaired cognitive skills (reaction time, perceptual speed), impaired manual dexterity
Laine et al. 1996									
2	Human 9 M	5 hours	200 (TWA)	BI, CS	Neuro	200			
Mackay et al. 1987									
3	Human 12 M	3.5 hours	0, 175, 350	CS, NX	Neuro		175[b]		Impaired performance on measures of cognitive skills (simple reaction time, four choice reaction time, task tracking: target acquisition, root mean squared error, and time on target)
NIOSH 1975									
4	Human 10 M, 10 F	5 days 1–7.5 hours/day	0, 100 (M), 350 (M, F), 500 (M)	BC, CS, NX, UR	Resp	350 F 500 M			
					Hemato	350 F 500 M			
					Hepatic	350 F 500 M			
					Neuro	350	500 M		Altered EEG tracings: increased amplitude of alpha activity on the final day
					Renal	500			

Table 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Salvini et al. 1971									
5	Human 6 M	1 day 8 hours/day	0, 450	CS, NX	Neuro	450			
Savolainen et al. 1981									
6	Human 4–5 M	1 day 4 hours/day	0, 200, 400	CS, NX	Neuro	400			
Stewart et al. 1961									
7	Human 2–7 M	1 day 15–186 minutes/ day	0, 500, 900, 910, 955, 0–2,650[c]	BC, CS, UR	Resp		1,900		Throat irritation (subjective) in 6/7 subjects
					Hepatic	2,650			
					Neuro	496	900		Lightheadedness (subjective) in 2/6 subjects
					Renal	2,650			
Stewart et al. 1969									
8	Human 5 M	5 days 6.5–7 hours/day	500	CS	Neuro	500			
Geller et al. 1982									
9	Monkey (baboon) 4 M	4 hours	0, 700, 1,400, 1,800, 2,100	CS, NX	Neuro	1,400	1,800		Impaired performance in learning and memory in a match to sample test
Adams et al. 1950									
10	Rat (Wistar) 3–17 M	6–420 minutes	0, 5,000, 10,000, 12,000,	BW, CS, GN, HP, OW	Death				LC_{50} (3 hours): 18.000 ppm LC_{50} (7 hours): 14,250 ppm
					Bd wt	18,000			
					Cardio	18,000			

Table 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
			15,000, 18,000, 30,000		Hepatic		8,000		Increase in relative liver weight; slight fatty changes of the liver
					Renal	18,000			
					Neuro			5,000	Narcosis
BRRC 1987a									
11	Rat (CD) 30 F	GDs 6–15 4 hours/day	0, 1,000, 3,000, 6,000	CS, BW, OW, FI, WI, HP, DX	Develop	3,000	6,000		6% decrease in female fetal weight, delayed ossification was observed in 15 pups
Calhoun et al. 1981									
12	Rat (CDF) 5 M, 5 F	6 hours	0, 4,946	BC, BW, GN, OW	Bd wt	4,946			
					Ocular		4,946		Porphyrin like pigmentation around eyes
					Neuro		4,946		Motor incoordination
Carlson 1973									
13	Rat (Albino) 5 M	2 hours	0, 11,600	BI, BW, BC, OF	Hepatic	11,600			
Carlson 1973									
14	Rat (Albino) 5 M	2 hours	0, 13,070	BI, BW, BC, OF	Hepatic	13,070			
Cornish and Adefuin 1966									
15	Rat (Sprague-Dawley) 6 M	2 hours	0, 10,000, 15,000	HP, BC, CS	Bd wt	15,000			
					Resp	15,000			
					Hepatic	15,000			
					Renal	15,000			
					Immuno	15,000			
					Endocr	15,000			

Table 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Folbergrova et al. 1984									
16	Rat (Wistar) 6 M	5 or 60 minutes	0, 8,000	BI, CS, NX	Cardio		8,000		Decreased mean arterial blood pressure
					Neuro	8,000			
Fuller et al. 1970									
17	Rat (Sprague-Dawley) 10 M	24 hours	0, 2,500–3,000	BI, CS, OF	Hepatic		2,500		Increased absolute and relative liver weight
George et al. 1989									
18	Rat (Wistar) 30 NS	8 hours	0, 3000, 4800, 6400, 9600, 12000, 20000	CS	Neuro		3,000	4,800	LOAEL: Lethargy SLOAEL: Anesthesia
Hougaard et al. 1984									
19	Rat (Wistar) 6–11 M	0.5–2 hours	0, 3,500, 6,000, 7,800	NX	Neuro	3,500	6,000	7,800	LOAEL: 14–55% decrease in local cerebral glucose consumption, ”intoxication signs,” decreased motility and exploration SLOAEL: Ataxia
Koizumi et al. 1983									
20	Rat (Wistar) 6 M	10 days 24 hours/day	0, 200, 400, 800	BW, OW, BC, BI	Hepatic		200		Increase in relative liver weight

Table 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Mullin and Krivanek 1982									
21	Rat (Charles River-CD) 6 M	0.5–4 hours	0, 1,750, 3,080, 6,100, 11,550	CS, NX	Death			11,550	2/6 died
					Resp			6,100	Respiratory distress
					Neuro	1,750		3,080	Ataxia and impaired placing, grasping, lift, and righting reflexes
Savolainen et al. 1977									
22	Rat (Sprague-Dawley) 10 M	4 days 6 hours/day 0, 2, 3, 4, or 6 hours of exposure on 5th day	0, 500	BI, CS, NX	Hepatic	500			
					Neuro	500			
Schwetz et al. 1975									
23	Rat (Sprague-Dawley) 23–30 F	10 days (GDs 6–15), 7 hours/day	0, 875	BW, CS, DX, OW, RX	Bd wt	875			
					Hemato	875			
					Hepatic	875			
					Repro	875			
					Develop	875			
Aranyi et al. 1986									
24	Mouse (CD-1) 140 F	3 hours	0, 350	CS, OF	Immuno	350			
Balster et al. 1982									
25	Mouse (CD-1) 8 M	20 minutes	0, 1,000, 2,000, 4,000, 8,000	CS, NX, OF	Neuro	1,000	2,000		Impaired operant learning

Table 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Bowen and Balster 1996									
26	Mouse (CFW) 10 M	5 days 30 minutes/day	0, 500, 1,250, 2,500, 5,000, 7,500, 10,000	CS, NX	Neuro		1,250		Increase in locomotor activity
Bowen and Balster 1996									
27	Mouse (CFW) 10 M	5 days 30 minutes/day	0, 500, 1,250, 2,500, 5,000, 7,500, 10,000, 12,500	CS, NX	Neuro		2,500		Increase in motor activity
Bowen and Balster 1998									
28	Mouse (albino) 10 M	2 days 30 minutes/day	0, 500, 1,000, 2,000, 4,000, 6,000, 8,000, 10,000, 12,000, 14,000	CS, NX	Neuro	2,000	4,000		Increase in locomotor activity

Table 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Bowen and Balster 1998									
29	Mouse (albino) 7 M	2 days 30 minutes/day	0 1,000, 2,000, 4,000, 8,000, 10,000, 12,000	BI, NX	Neuro	2,000	4,000		Impaired operant learning
Bowen and Balster 2006									
30	Mouse (Albino) 40 M	30 minutes	0, 2,000, 6,000, 10,000, 13,300	NX	Neuro	2,000	6,000		Increase in locomotor activity
Bowen et al. 1996a									
31	Mouse (albino) 10 M	30 minutes	0, 2,500, 5,000, 10,000	CS, NX	Neuro	5,000	10,000		Hyperactivity in elevated plus maze
Bowen et al. 1996b									
32	Mouse (albino) 8 M	20 minutes	0, 4,000, 8,000, 10,000, 13,300, 18,000	CS, NX	Neuro	8,000		10,000	Impaired motor coordination/ strength (inverted screen test), impaired gait and righting reflex
Calhoun et al. 1981									
33	Mouse (B6C3F1) 5 M, 5 F	6 hours	0, 4,946	BC, BI, BW, GN, OW, OF	Bd wt	4,946			
					Ocular	4,946			
					Neuro	4,946			

Table 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Evans and Balster 1993									
34	Mouse (CFW Swiss) 10 M	4 days 24 hours/day	0, 500, 1,000, 2,000, 4,000	CS, BW, NX, OP	Bd wt	2,000		4,000	25% decrease in body weight 96 hours after exposure
					Dermal	2,000	4,000		Dull fur coat
					Ocular	2,000	4,000		Eye irritation observed
					Neuro			500	5/10 experienced withdrawal convulsions upon handling after exposure
Jones et al. 1996									
35	Mouse (CD-1) 12	5 days (GDs 12–17), 3 exposures/day 60 minutes/ exposure	0, 8,000	BW, CS, DX, FI, NX, RX, WI	Bd wt	8,000			
					Neuro			8,000	Sedation, splayed hindlimb, clonic movements, severe sway, ataxia, and gait abnormalities in dams
					Repro	8,000			
					Develop			8,000	Decrease in litter weight on PNDs 2–19; delayed eye opening, Impaired righting reflex
Jones et al. 1996									
36	Mouse (CD-1) 10 F	6 days (GDs 12–17), 17 hours/day	0, 2,000	BW, CS, DX, FI, NX, RX, WI	Bd wt	2,000			
					Develop			2,000	Decreased litter weight; delayed eye opening in pups; impaired righting reflex; decrease in grip strength; delay in negative geotaxis
Kjellstrand et al. 1985a									
37	Mouse (NMRI) 14–54 M	1 hour	0,700, 900, 1,200, 2,300	CS	Neuro	900	1,200		Increase in motor activity

Table 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Moser and Balster 1986									
38	Mouse (CD-1) 15 M	30 minutes	0, 1,800, 3,600, 7,200, 10,800	CS, NX	Neuro	3,600	7,200		Impaired operant learning
Ohnishi et al. 2013									
39	Mouse (C57Bl/ 6J) 6 M	5 days 6 hours/day	0, 5, 50, 500	BI, HP	Repro	500			
Páez-Martínez et al. 2003									
40	Mouse (Swiss-Webster) 12	30 minutes	0, 2,000, 4,000, 8,000, 10,000	CS, NX	Neuro	4,000	8,000		Decreased anxiety in conditioned defensive burying
Schwetz et al. 1975									
41	Mouse (Swiss Webster) 13–30 F	10 days (GDs 6–15), 7 hours/day	0, 875	BW, CS, DX, OW, RX	Bd wt	875			
					Hemato	875			
					Hepatic	875			
					Repro	875			
					Develop	875			
Woolverton and Balster 1981									
42	Mouse (CD-1) 12 M	30 minutes	0, 3,600–23,000	CS, LE, NX, OF	Death			22,241	6/12 mice died
					Neuro		7,000		Impaired motor coordination/strength (inverted screen test)

Table 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Egle et al. 1976									
43	Dog (Beagle) 6 M, 6 F	15 minutes	0, 5,000, 10,000	CS	Cardio	10,000			
					Neuro	10,000			
Herd et al. 1974									
44	Dog (NS) 9 NS	5 minutes	0, 8,000, 15,000, 20,000, 25,000	CS, GN, HP, NX, OF	Cardio			8,000	50 mm Hg reduction in mean arterial blood pressure
					Hepatic	25,000			
					Neuro	25,000			
BRRC 1987b									
45	Rabbit (New Zealand) 24 F	12 days (GDs 618) 6 hours/day	0, 1,000, 3,000, 6,000	BW, DX, OW, RX	Bd wt	6,000			
					Hepatic	6,000			
					Repro	1,000			
					Develop	3,000	6,000		42/72 fetuses (18/20 litters) showed bilateral 13th rib
INTERMEDIATE EXPOSURE									
MacEwen and Vernot 1974									
46	Monkey (NS) 4 NS	14 weeks 7 days/week 24 hours/day	0, 250, 1,000	GN, HP, BC	Bd wt	1,000			
					Resp	1,000			
					Hemato	1,000			
					Hepatic	1,000			
					Renal	1,000			

Table 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Prendergast et al. 1967									
47	Monkey (Squirrel) 3 NS	6 weeks 5 days/week 8 hours/day	0, 2,210	BW, GN, HP, CS	Bd wt	2,210			
					Resp	2,210			
					Cardio	2,210			
					Hepatic	2,210			
					Renal	2,210			
					Immuno	2,210			
					Neuro	2,210			
Prendergast et al. 1967									
48	Monkey (Squirrel) 3 NS	90 days 24 hours/day	0, 140, 380	BW, GN, HP	Bd wt	380			
					Resp	380			
					Cardio	380			
					Hepatic	380			
					Renal	380			
					Immuno	380			
Torkelson et al. 1958									
49	Monkey (NS) 2 F	6 months 5 days/week 7 hours/day	0, 500		Resp	500			
					Cardio	500			
					Hemato	500			
					Hepatic	500			
					Renal	500			
					Immuno	500			

Table 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Adams et al. 1950									
50	Rat (Wistar) 6 M, 7 F	67 days 5 days/week 7 hours/day	0, 3,000	BW, CS, GN, HP, OW	Bd wt	3,000			
					Cardio	3,000			
					Hepatic	3,000			
					Renal	3,000			
					Repro	3,000			
Adams et al. 1950									
51	Rat (Wistar) 5 M, 5 F	44 days 5 days/week 7 hours/day	0, 5,000	BW, CS, GN, HP, OW	Bd wt	5,000			
					Resp	5,000			
					Cardio	5,000			
					Hepatic	5,000			
					Renal	5,000			
					Repro	5,000			
Calhoun et al. 1981									
52	Rat (CDF) 28 M, 28 F	13 weeks 5 days/week 6 hours/day	0, 150, 508, 1,008, 1,976	BC, BI, BW, GN, HP, OW, UR	Bd wt	1,976			
					Resp	1,008	1,976		Degenerative changes in the olfactory epithelium of the nasal turbinates; 10/10 males 10/10 females
					Cardio	1,976			
					Gastro	1,976			
					Hemato	1,976			
					Musc/skel	1,976			
					Hepatic	1,008			
					Renal	1,976			
					Dermal	1,976			

Table 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Ocular	1,976			
					Immuno	1,976			
					Neuro	1,976			
					Repro	1,976			
MacEwen and Vernot 1974									
53	Rat (NS) 40 NS	14 weeks 24 hours/day	0, 250, 1,000	BW, OW, GN, HP	Bd wt	1,000			
					Resp	1,000			
					Hepatic	1,000			
					Renal	1,000			
Mattsson et al. 1993									
54	Rat (Fischer 344) 14 M, 14 F	13 weeks 5 days/week 6 hours/day	0, 209, 620, 2,016	BW, CS, GN, HP, OF	Bd wt	2,016			
					Neuro	620	2,016		Impaired forelimb grip strength
Prendergast et al. 1967									
55	Rat (Sprague-Dawley) 15 NS	6 weeks 5 days/week 8 hours/day	0, 2,210	BW, GN, HP, BC	Bd wt	2,210			
					Resp	2,210			
					Cardio	2,210			
					Hemato	2,210			
					Hepatic	2,210			
					Renal	2,210			
					Immuno	2,210			
					Neuro	2,210			

Table 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Prendergast et al. 1967									
56	Rat (Sprague-Dawley) 1–5 NS	90 days 24 hours/day	0, 140, 380	BW, GN, HP, BC, CS	Bd wt	380			
					Resp	380			
					Cardio	380			
					Hemato	380			
					Hepatic	380			
					Renal	380			
					Immuno	380			
Toftgard et al. 1981									
57	Rat (Sprague-Dawley) 4 M	4 weeks 5 days/week 6 hours/day	0, 820	BW, OW, BI	Bd wt	820			
					Hepatic		820		Increased absolute and relative liver weights
Torkelson et al. 1958									
58	Rat (NS) 5 M, 5 F	6 months 5 days/week 7 hours/day	0, 500	BW, OW, GN, HP, BC	Bd wt	500			
					Resp	500			
					Cardio	500			
					Hemato	500			
					Hepatic	500			
					Renal	500			
					Immuno	500			
					Repro	500 M			

Table 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Torkelson et al. 1958									
59	Rat (NS) 5 M	3 months 5 days/week 3–60 minutes/day	0, 10,000	BW, OW, GN, HP, CS	Bd wt	10,000			
					Hepatic	10,000			
					Renal	10,000			
					Neuro			10,000	Ataxia, narcosis
Truffert et al. 1977									
60	Rat (Sprague-Dawley) 55 F	15 weeks 5 days/week 5–6 hours/day	0, 1,100	CS, BW, BC, GN, OW, HP	Bd wt	1,100			
					Resp	1,100			
					Hemato	1,100			
					Hepatic	1,100			
					Renal	1,100			
					Repro	1,100			
York et al. 1982									
61	Rat Long-Evans 11–20 F	Premating: 2 weeks 5 days/week 6 hours/day Pregnancy: 20 days (GDs 1–20), 7 days/week 6 hours/day	0, 2,100	CS, BW, FI, WI, HE, BC, OW, NX, RX, DX	Bd wt	2,100			
					Hepatic	2,100			
					Repro	2,100			
					Develop		2,100		Increased total skeletal anomalies 19/78 fetuses; reduced clavicle size in 5/78 fetuses; Increased soft tissue anomalies in 6/71 fetuses
Bowen and Balster 2006									
62	Mouse (Albino) 8 M	15 days 30 minutes/day	0, 2,000, 6,000, 10,000, 13,300	NX	Neuro	2,000	6,000		Increase in locomotor activity

Table 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Calhoun et al. 1981									
63	Mouse (B6C3F1) 20 M, 20 F	13 weeks 5 days/week 6 hours/day	0, 150, 508, 1,008, 1,976	BC, BI, BW, GN, HP, OW, UR	Bd wt	1,976			
					Resp	1,008	1,976		Olfactory epithelial changes in the nasal turbinates in 5/10 M and 6/10 F
					Cardio	1,976			
					Gastro	1,976			
					Hemato	1,976			
					Musc/skel	1,976			
					Hepatic	1,976			
					Renal	1,976			
					Dermal	1,976			
					Ocular	1,976			
					Immuno	1,976			
					Neuro	1,976			
					Repro	1,976			
MacEwen and Vernot 1974									
64	Mouse (NS) 3 NS	14 weeks 24 hours/day (NS)	0, 250, 1,000	BI, HP	Bd wt	1,000			
					Hepatic	250	1,000		Increased centrilobular fat accumulation; increase in liver triglycerides
McNutt et al. 1975									
65	Mouse (CF1) 10 M	14 weeks 24 hours/day	0, 250, 1,000	BW, OW, FI, WI, GN, HP, CS, BI	Hepatic	250	1,000		Increase in relative liver weight; increase in liver triglycerides; hepatocyte vacuolation, degeneration, and necrosis

Table 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
MacEwen and Vernot 1974									
66	Dog (NS) 8 NS	14 weeks 24 hours/day	0, 250, 1,000	GN, HP, BC	Gastro	1,000			
					Hemato	1,000			
					Hepatic	1,000			
					Renal	1,000			
Adams et al. 1950									
67	Guinea pig (NS) 5 M, 4 F	29 days 5 days/week 7 hours/day	0, 3,000	BW, CS, GN, HP, OW	Bd wt			3,000	13% decreased final body weight and 49% decrease in body weight gain in females; 12% decreased final body weight and 53% decrease in body weight gain in males
					Resp	3,000			
					Cardio	3,000			
					Hepatic	3,000			
					Renal	3,000			
					Immuno	3,000			
					Repro	3,000			
Adams et al. 1950									
68	Guinea pig (NS) 5 M, 5 F	45 days 5 days/week 7 hours/day	0, 5,000	BW, CS, GN, HP, OW	Bd wt			5,000	11% decrease final body weight and 33% decrease in body weight gain in females; 10% decrease in final body weight and 19% decrease in body weight gain in males
					Resp	5,000			
					Hepatic		5,000		8/8 had slight to moderate central fatty degeneration the liver

Table 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Renal	5,000			
					Immuno	5,000			
Adams et al. 1950									
69	Guinea pig 9 M, 10 F	93 days 5 days/week 7 hours/day	0, 650	BW, CS, GN, HP, OW	Bd wt	650 F		650 M	10% decrease in final body weight; 37% decrease in body weight gain
					Resp	650			
					Cardio	650			
					Hepatic	650			
					Renal	650			
					Immuno	650			
					Repro	650			
Adams et al. 1950									
70	Guinea pig 8 M, 6 F	58 days 5 days/week 7 hours/day	0, 650	BW, CS, GN, HP, OW	Bd wt	650 M		650 F	11% decrease in final body weight; 35% decrease in final body weight gain
					Resp	650			
					Cardio	650			
					Hepatic	650			
					Renal	650			
					Immuno	650			
					Repro	650			
Adams et al. 1950									
71	Guinea pig 12 M, 7–8 F	60 days 5 days/week 7 hours/day	0, 1,500	BW, CS, GN, HP, OW	Bd wt	1,500			
					Resp	1,500			
					Cardio	1,500			
					Hepatic	1,500			

Table 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Renal	1,500			
					Immuno	1,500			
					Repro	1,500			
Prendergast et al. 1967									
72	Guinea pig (Hartley) 15 NS	90 days 24 hours/day	0, 140, 380	BW, GN, HP, BC, CS	Bd wt	380			
					Resp	380			
					Cardio	380			
					Hemato	380			
					Hepatic	380			
					Renal	380			
					Immuno	380			
Prendergast et al. 1967									
73	Guinea pig (Hartley) 15 NS	6 weeks 5 days/week 8 hours/day	0, 2,210	BW, GN, HP, BC, CS	Bd wt	2,210			
					Resp	2,210			
					Cardio	2,210			
					Hemato	2,210			
					Hepatic	2,210			
					Renal	2,210			
					Immuno	2,210			
					Neuro	2,210			
Rosengren et al. 1985									
74	Gerbil (Mongolian) 4 M, 4 F	3 months 24 hours/day	0, 70, 210, 1,000	BI, BW, CS, NX, OF	Bd wt	1,000			
					Neuro	70[d]		210	Reactive gliosis (increase in GFAP)

Table 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Torkelson et al. 1958									
75	Guinea pig (NS) 8 M, 8 F	6 months 5 days/week 7 hours/day	0, 500	BW, OW, GN, HP, BC, CS	Bd wt	500			
					Resp	500			
					Gastro	500			
					Hepatic	500			
					Renal	500			
					Immuno	500			
					Repro	500			
Torkelson et al. 1958									
76	Guinea pig (NS) 5 F	3 months 5 days/week 18–180 minutes/day	0, 1,000, 2,000	OW, GN, HP, BW	Bd wt	2,000			
					Resp		1,000		Lung irritation and inflammation
					Hepatic		1,000		Increased relative liver weight; centrilobular fatty change
					Renal	2,000			
CHRONIC EXPOSURE									
Kramer et al. 1978									
77	Human 19–53	Up to 6 years (occupational)	0, <15, 15–49, 50–99, 100–149, 150–249 (TWA)	BC, CS	Cardio	150			
					Hemato	150			
					Hepatic	150			
					Renal	150			
Maroni et al. 1977									
78	Human 7–8 F	6.7 years average (occupational)	0, 110, 140–160, 200–990	CS	Neuro	200			

Table 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Ohnishi et al. 2013									
79	Rat (Fischer-344) 50 M, 50 F	104 weeks 5 days/week 6 hours/day	0, 200, 797, 3,181	LE, CS, BW, FI, BC, UR, GN, HP, OW	Bd wt	3,181			
					Resp	3,181			
					Hemato	3,181			
					Renal	3,181			
					Neuro	3,181			
					Other noncancer	3,181			
					Cancer			3,181 M	CEL: mesothelioma in the peritoneum in 16/50
Quast et al. 1988									
80	Rat (Fischer 344) 80 M, 80 F	2 years 5 days/week 6 hours/day	0, 150, 500, 1,500	BW, OW, GN, HP, BC, UR, CS	Bd wt	1,500			
					Resp	1,500			
					Cardio	1,500			
					Gastro	1,500			
					Hemato	1,500			
					Musc/skel	1,500			
					Hepatic	500	1,500		Mild liver histopathology-accentuation of the normal hepatic lobular pattern, alteration in the size of the hepatocytes
					Renal	1,500			
					Immuno	1,500			
					Neuro	1,500			
					Repro	1,500			

Table 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Ohnishi et al. 2013									
81	Mouse (BDF1) 50 M, 50 F	104 weeks 5 days/week 6 hours/day	0, 201, 801, 3,204	BC, BW, CS, FI, GN, HP, LE, OW, UR	Death			3,204 M	18% decrease in survival
					Bd wt	3,204			
					Hemato	3,204			
					Hepatic	3,204			
					Renal	3,204			
					Ocular	3,204			
					Neuro	3,204			
					Other noncancer	3,204			
					Cancer	801 M		201 F	CEL: hepatocellular adenoma in 9/50 female mice
								3,204 M	CEL: malignant lymphoma of spleen observed in 9/50 mice; hepatocellular adenoma increased trend, harderian gland adenoma in 8/50
Quast et al. 1988									
82	Mouse (B6C3F1) 80 M, 80 F	2 years 5 days/week 6 hours/day	0, 150, 500, 1,500	BW, OW, GN, HP, BC, CS	Bd wt	1,500			
					Resp	1,500			
					Cardio	1,500			
					Gastro	1,500			
					Hemato	1,500			
					Musc/skel	1,500			
					Hepatic	1,500			
					Renal	1,500			
					Dermal	1,500			

Table 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Immuno	1,500			
					Neuro	1,500			
					Repro	1,500			

[a]The number corresponds to entries in Figure 2-2; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-2 Where such differences exist, only the levels of effect for the most sensitive sex are presented.
[b]Used to derive an acute-duration inhalation MRL of 1 ppm based on decreased performance in psychomotor tests. See Appendix A for more detailed information regarding the MRL.
[c]Anesthetic dose, 0 progressively to 2,650 ppm.
[d]Used to derive an intermediate-duration inhalation MRL of 0.7 ppm based on reactive gliosis measured by glial fibrillary acid protein. See Appendix A for more detailed information regarding the MRL.

BI = biochemical changes; BC = blood chemistry; Bd wt or BW = body weight; Cardio = cardiovascular; CEL = cancer effect level; CS = clinical signs; Develop = developmental; DX = developmental toxicity; EEG = electroencephalograph; Endocr = endocrine; F = female(s); FI = food intake; Gastro = gastrointestinal; GD = gestation day; GFAP = glial fibrillary acid protein; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathological; Immuno = immunological; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); MRL = Minimal Risk Level; Musc/skel = musculoskeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; NX = neurological function; OF = organ function; OW = organ weight; PND = postnatal day; Repro = reproductive; Resp = respiratory; RX = reproductive toxicity; SLOAEL = serious LOAEL; TWA = time-weighted average; UR = urinalysis; WI = water intake

Figure 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation
Acute (≤14 days)

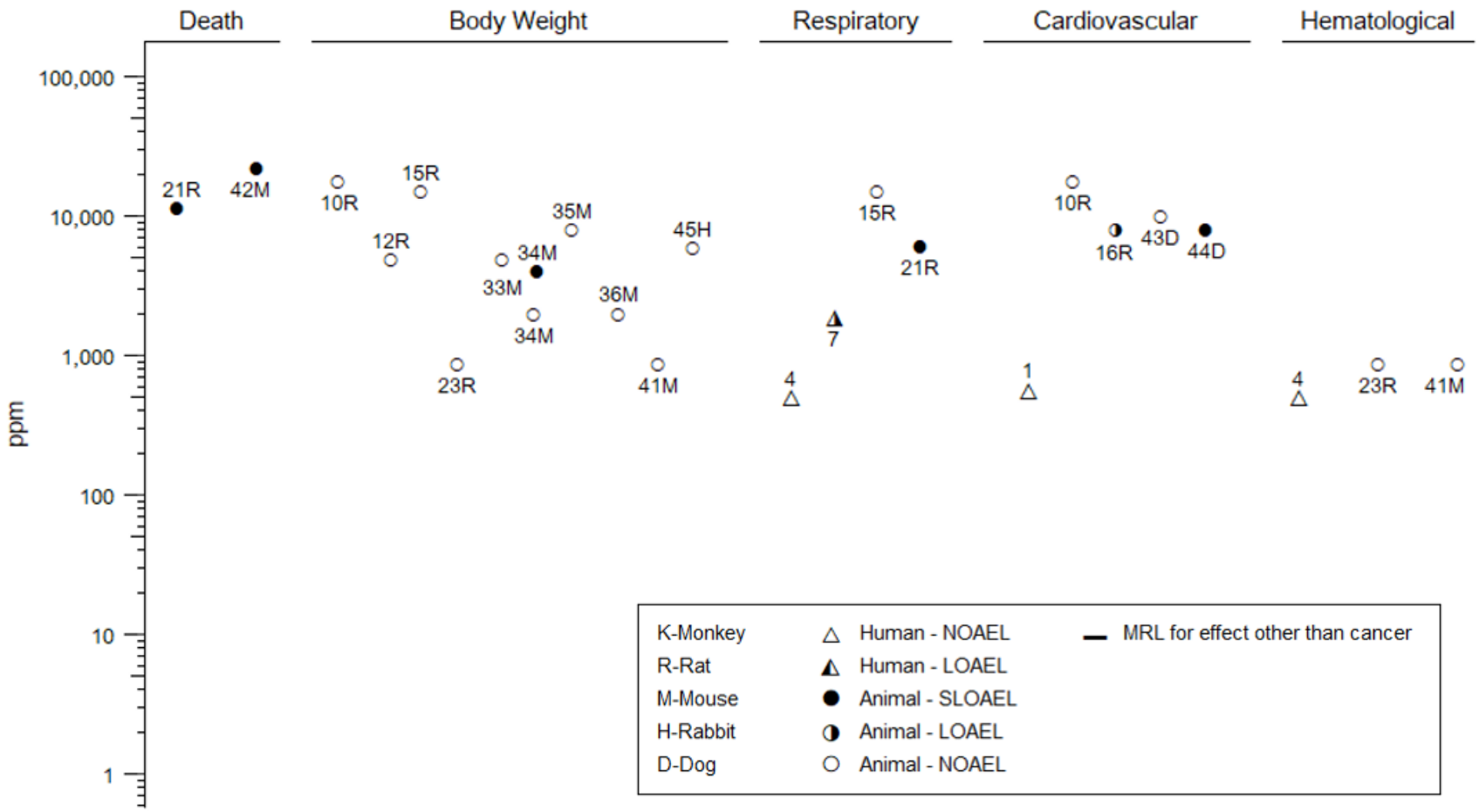


Figure 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation
Acute (≤14 days)

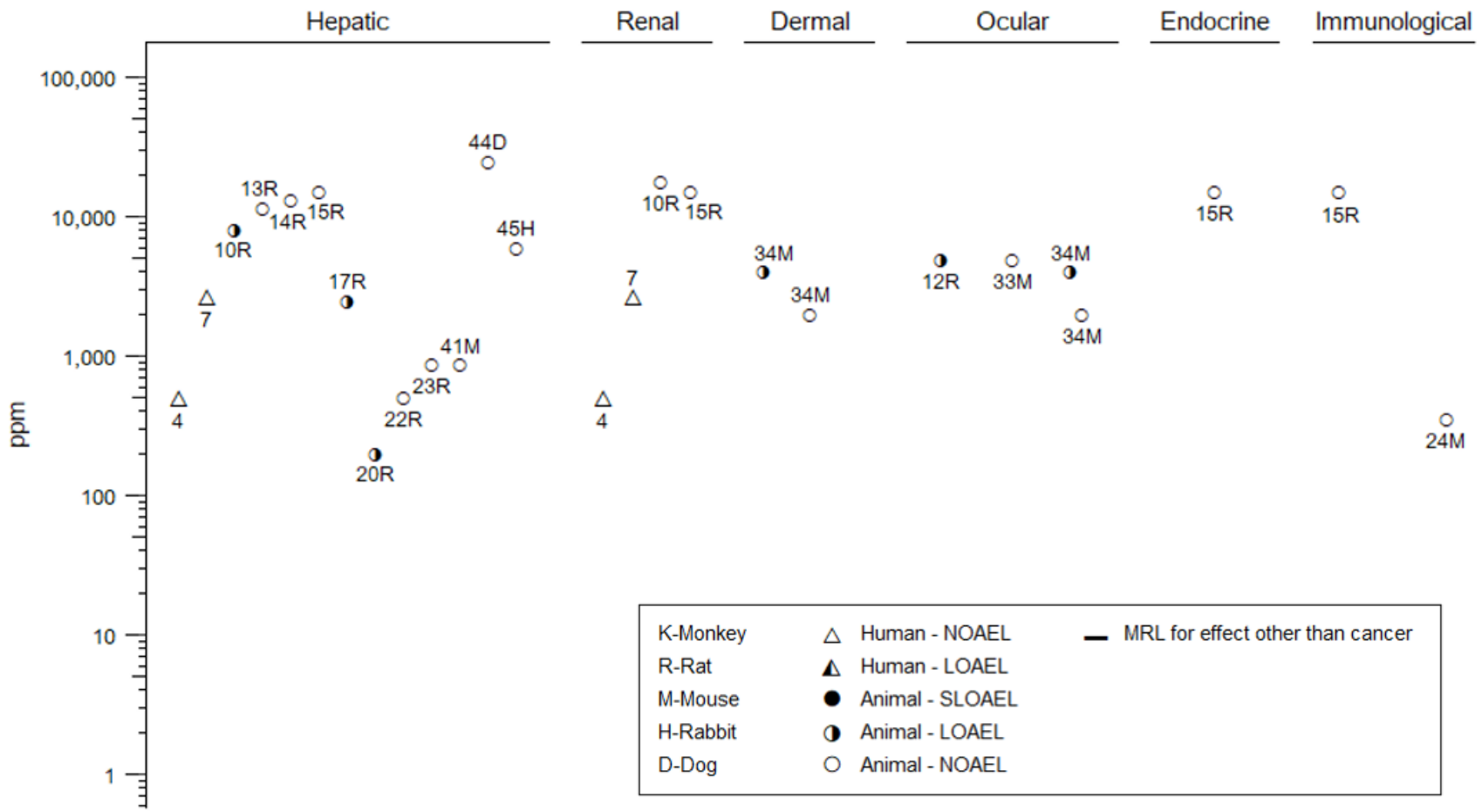


Figure 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation
Acute (≤14 days)

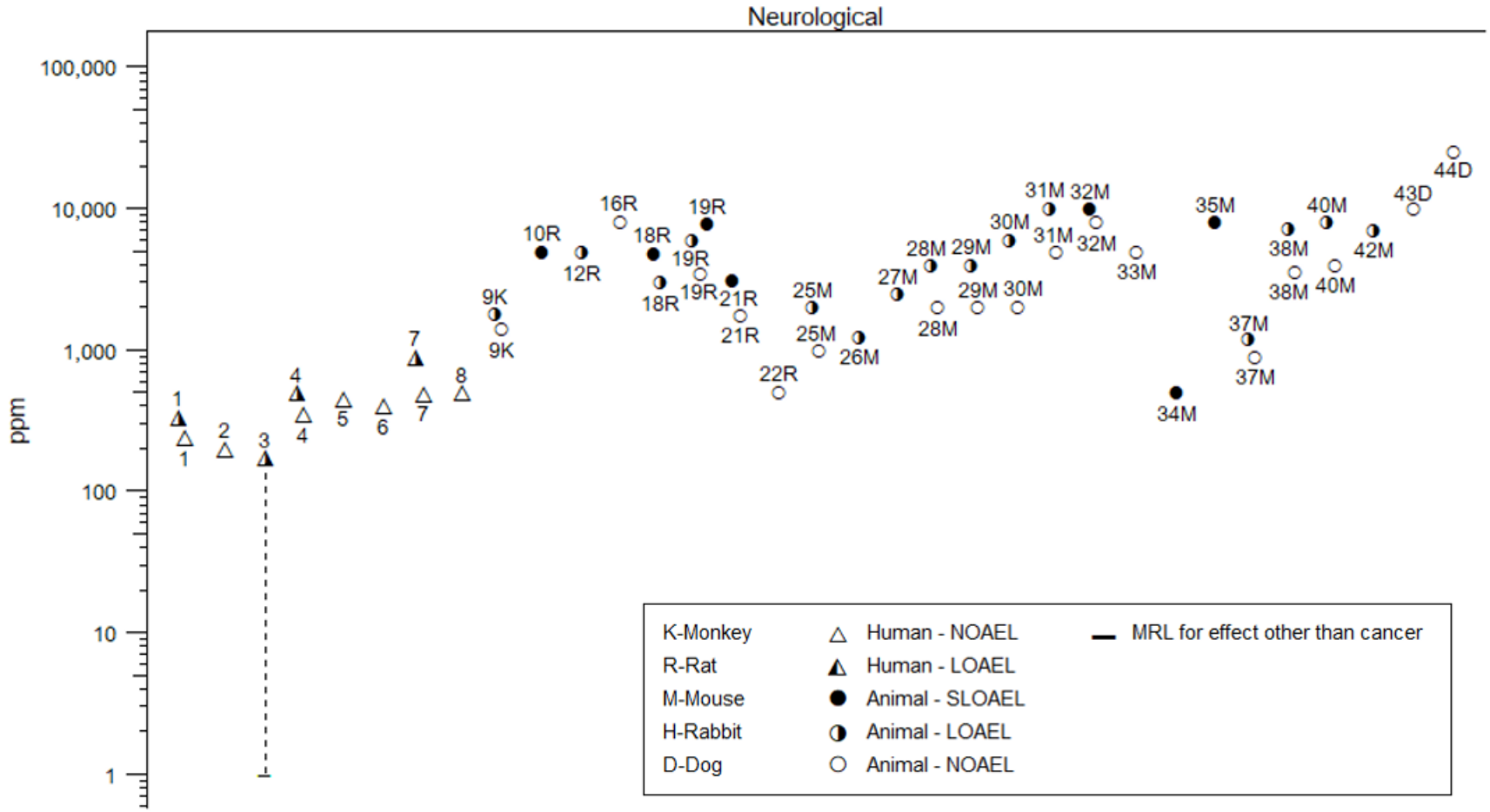


Figure 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation
Acute (≤14 days)

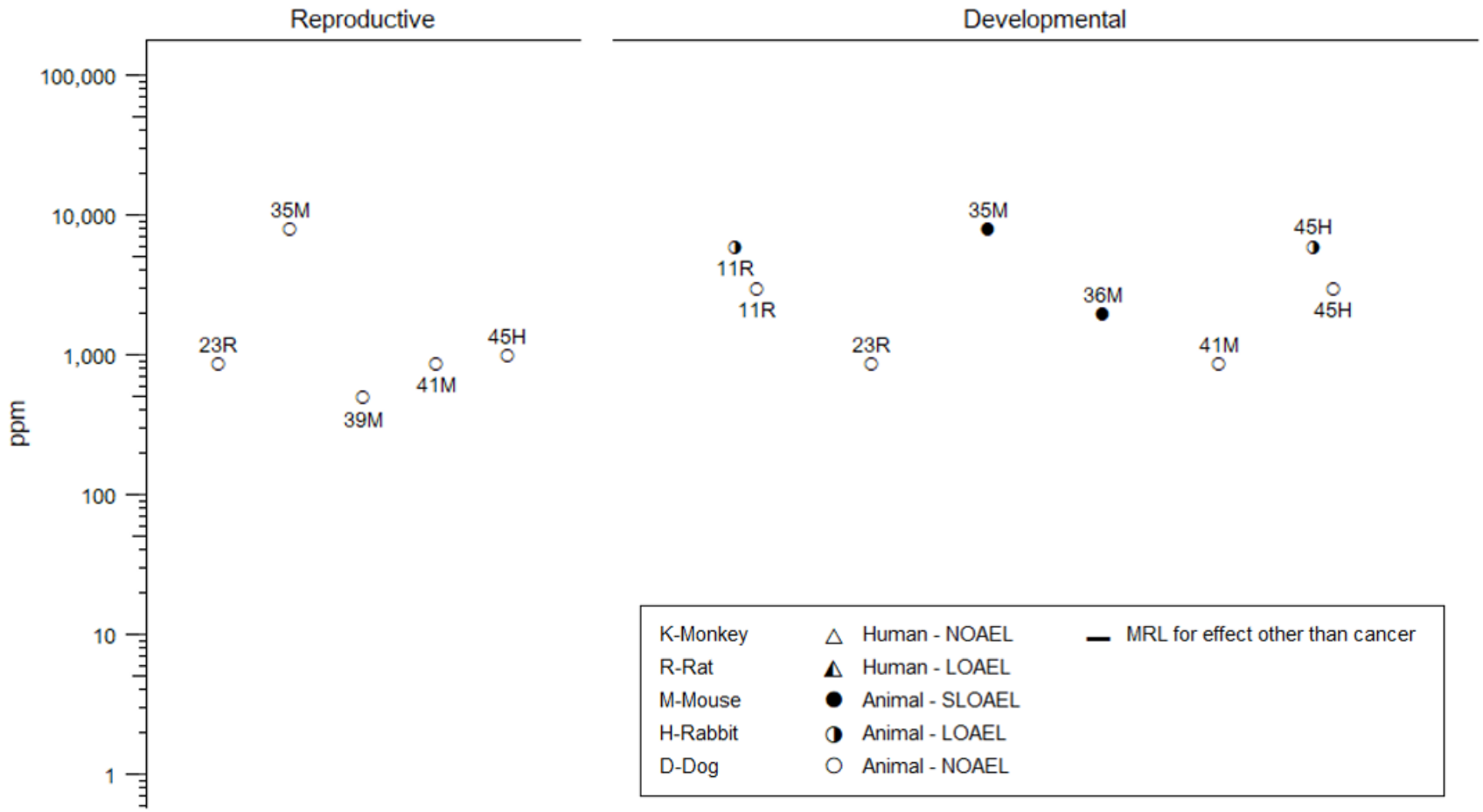


Figure 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation
Intermediate (15–364 days)

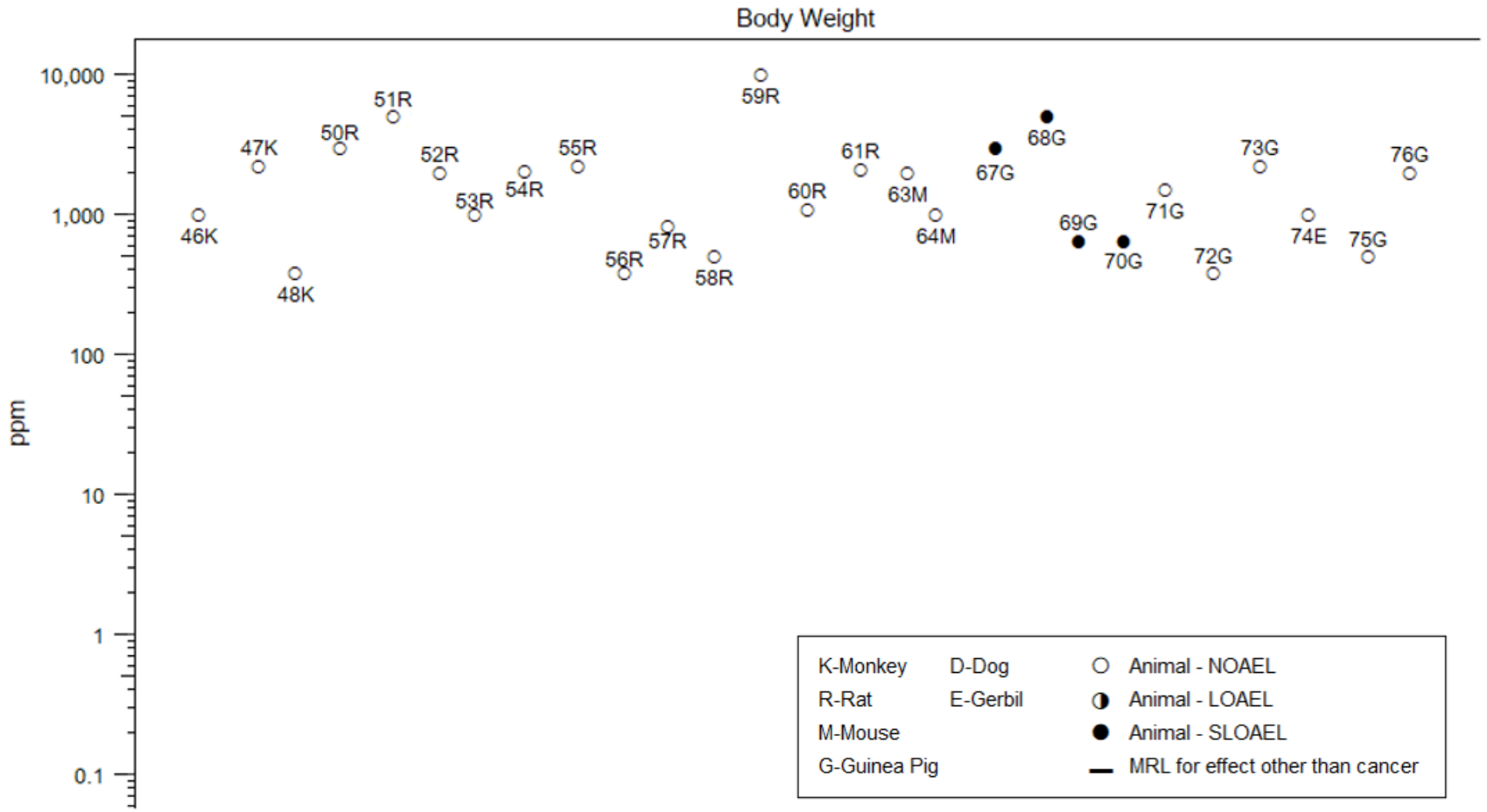


Figure 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation
Intermediate (15–364 days)

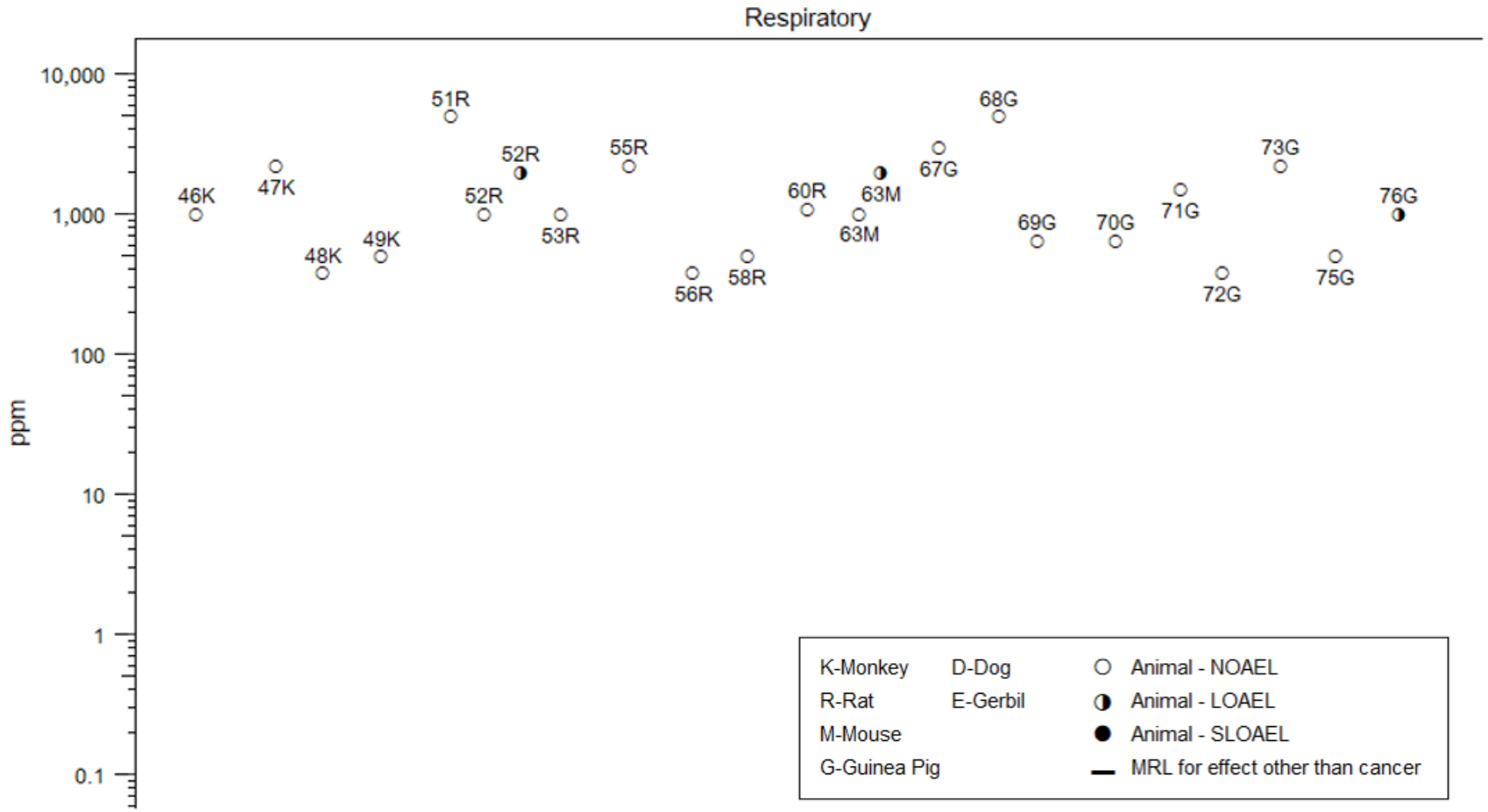


Figure 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation
Intermediate (15–364 days)

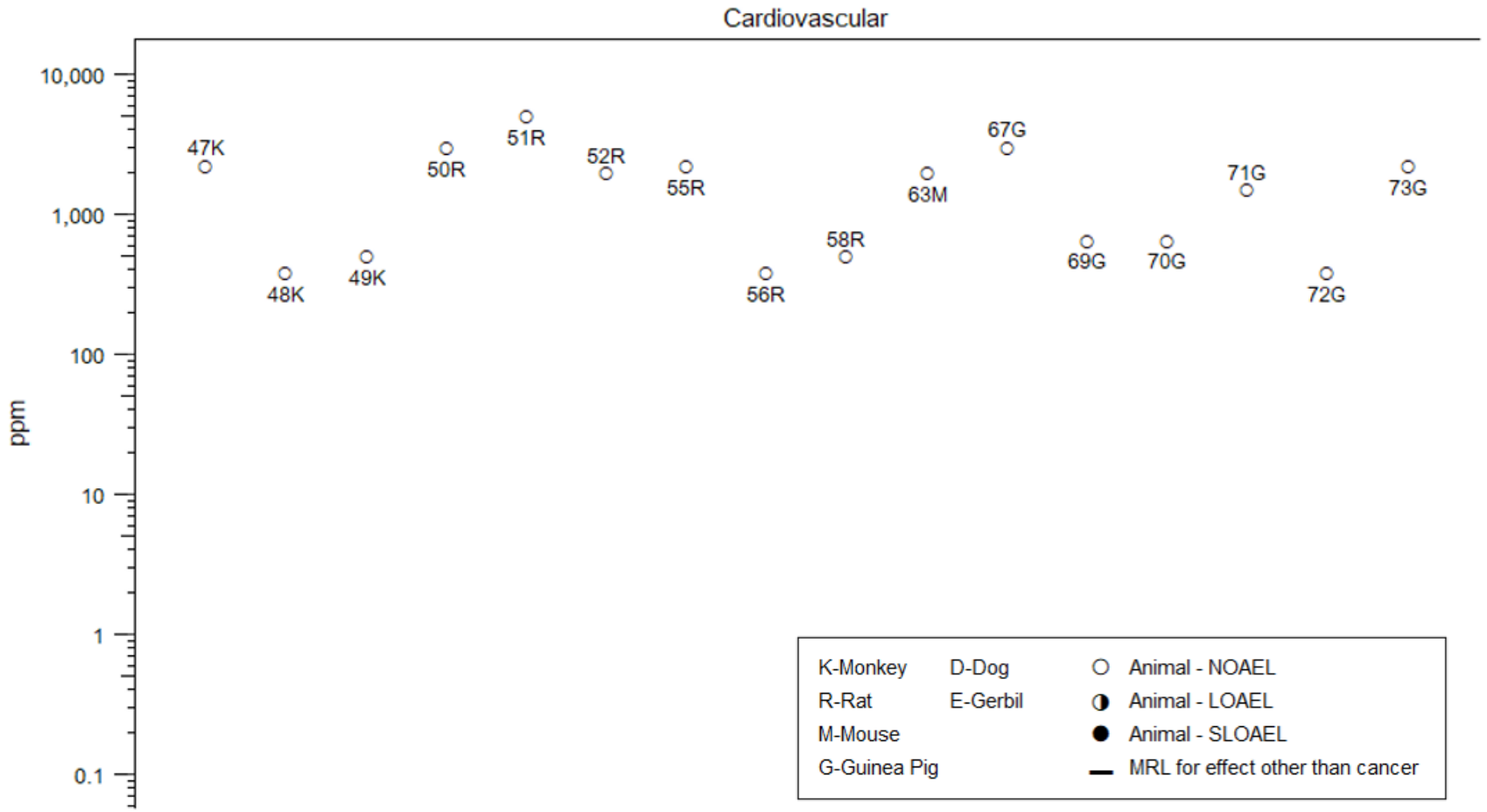


Figure 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation
Intermediate (15–364 days)

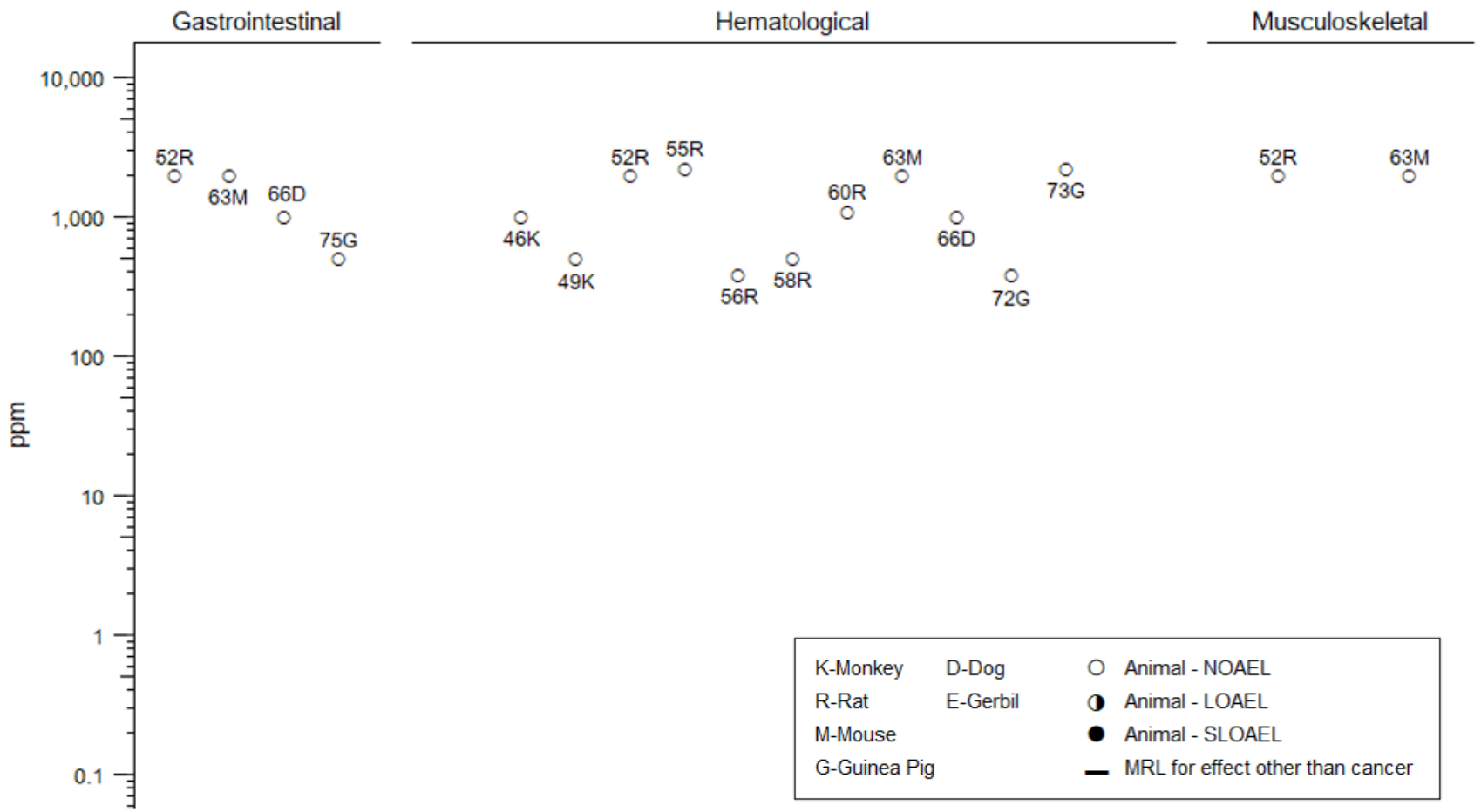


Figure 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation
Intermediate (15–364 days)

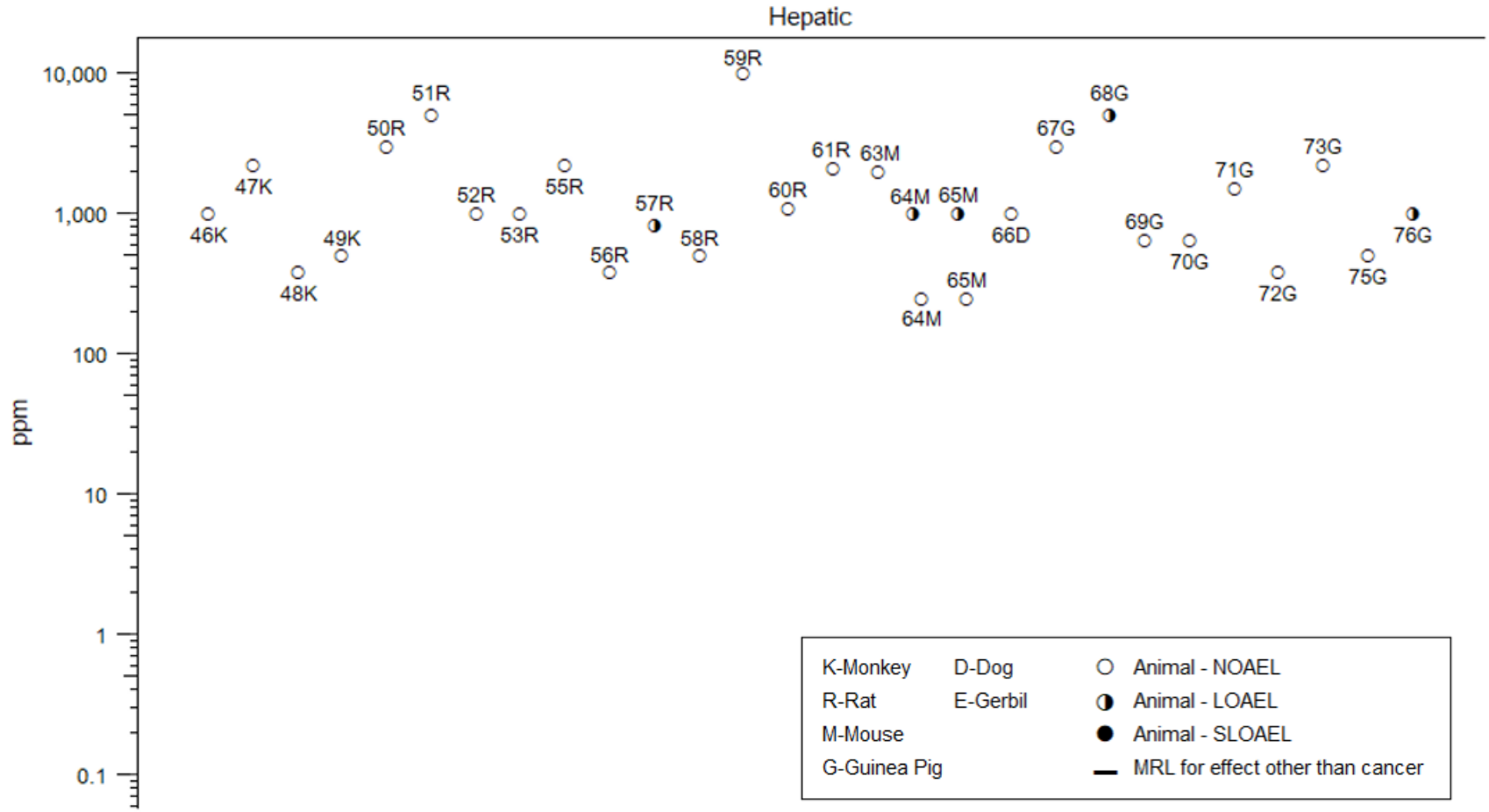


Figure 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation
Intermediate (15–364 days)

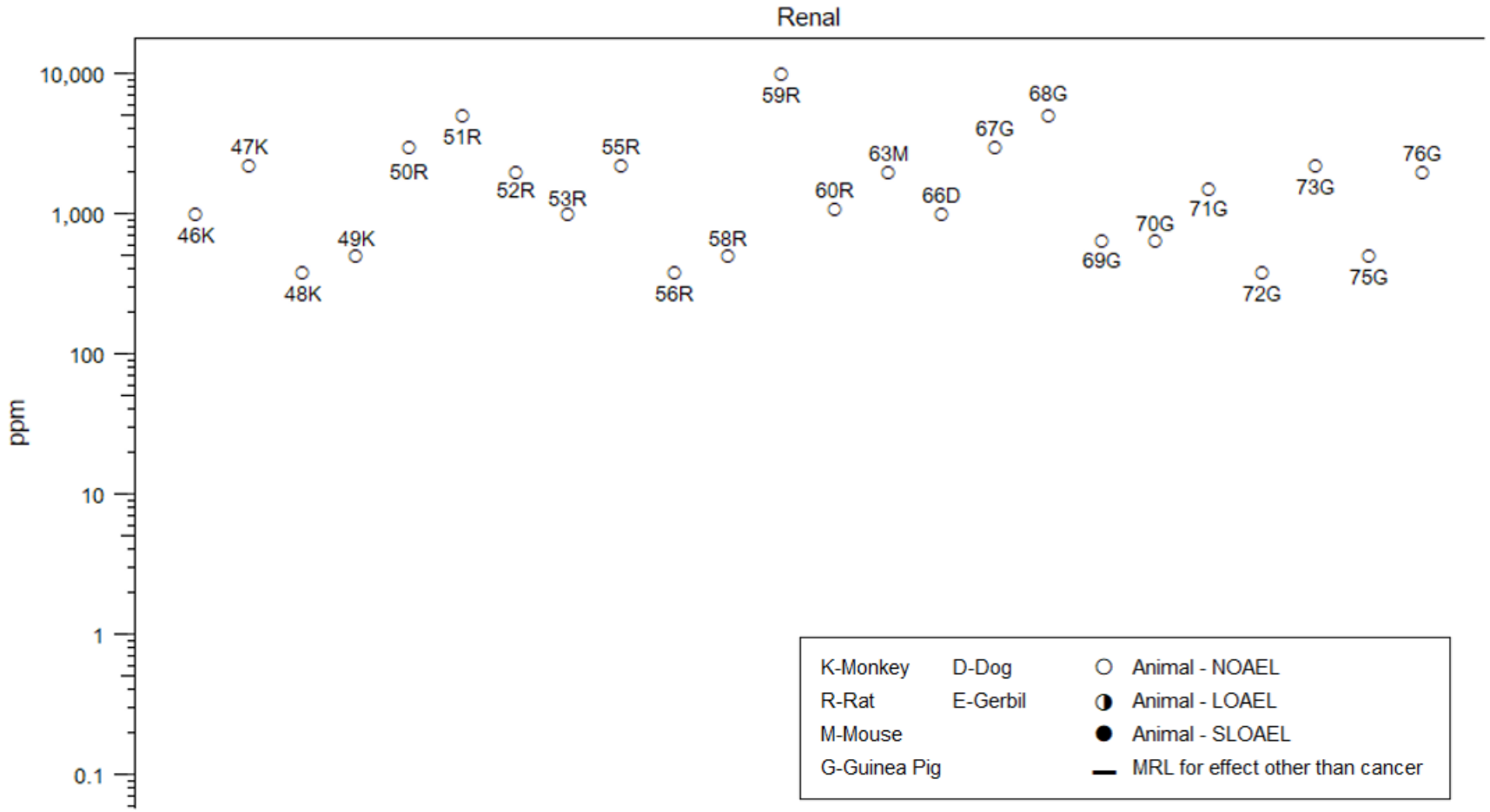


Figure 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation
Intermediate (15–364 days)

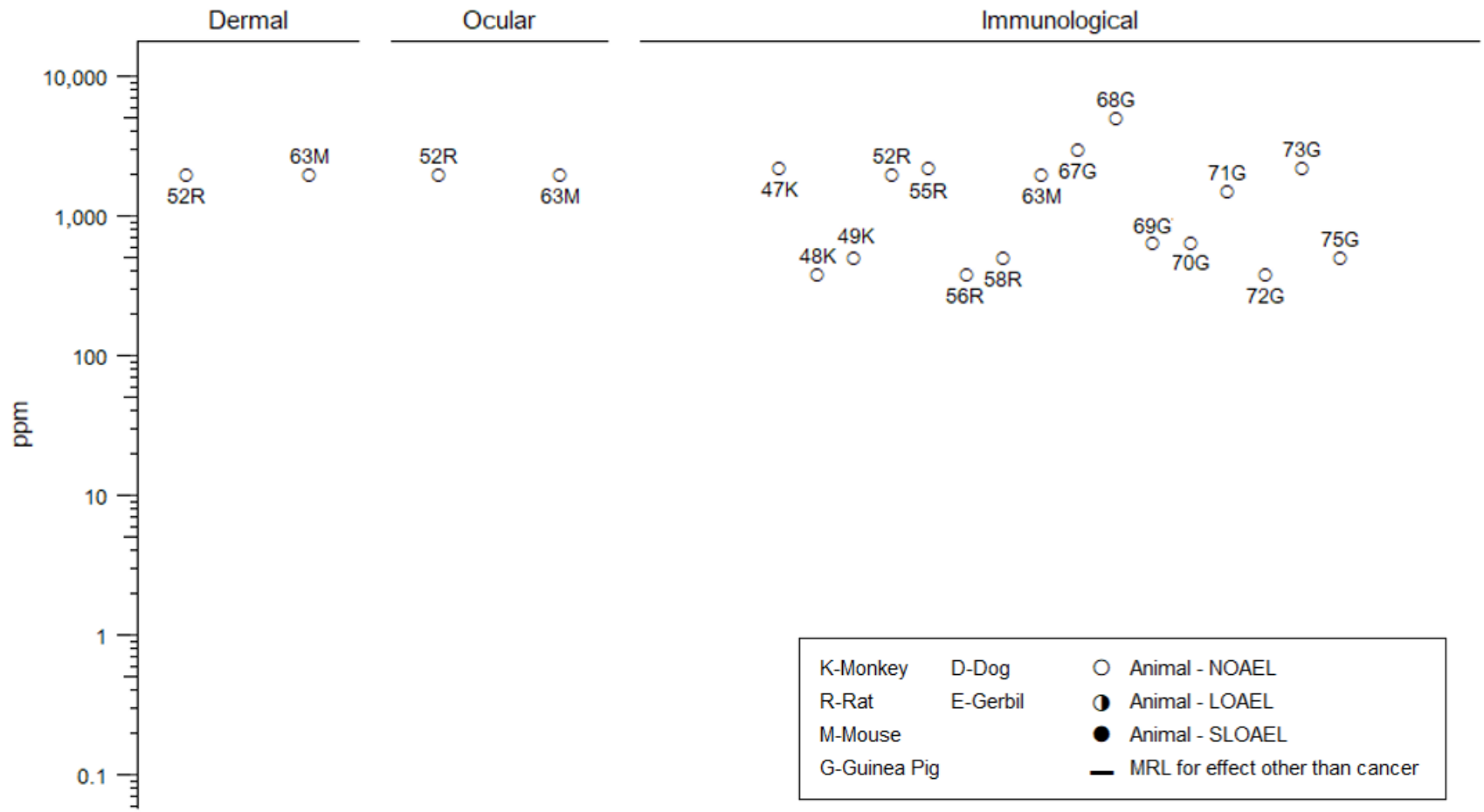


Figure 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation
Intermediate (15–364 days)

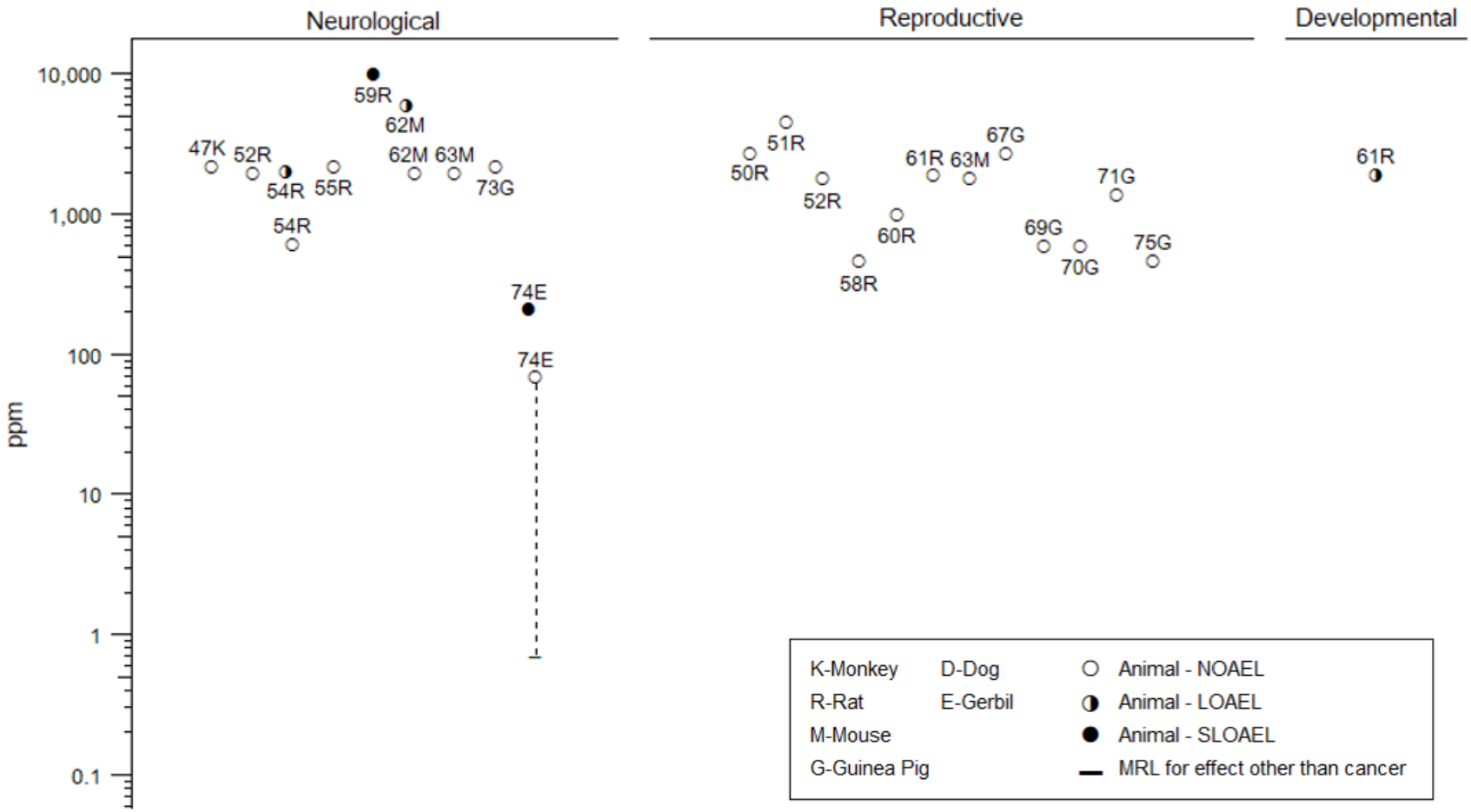


Figure 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation
Chronic (≥365 days)

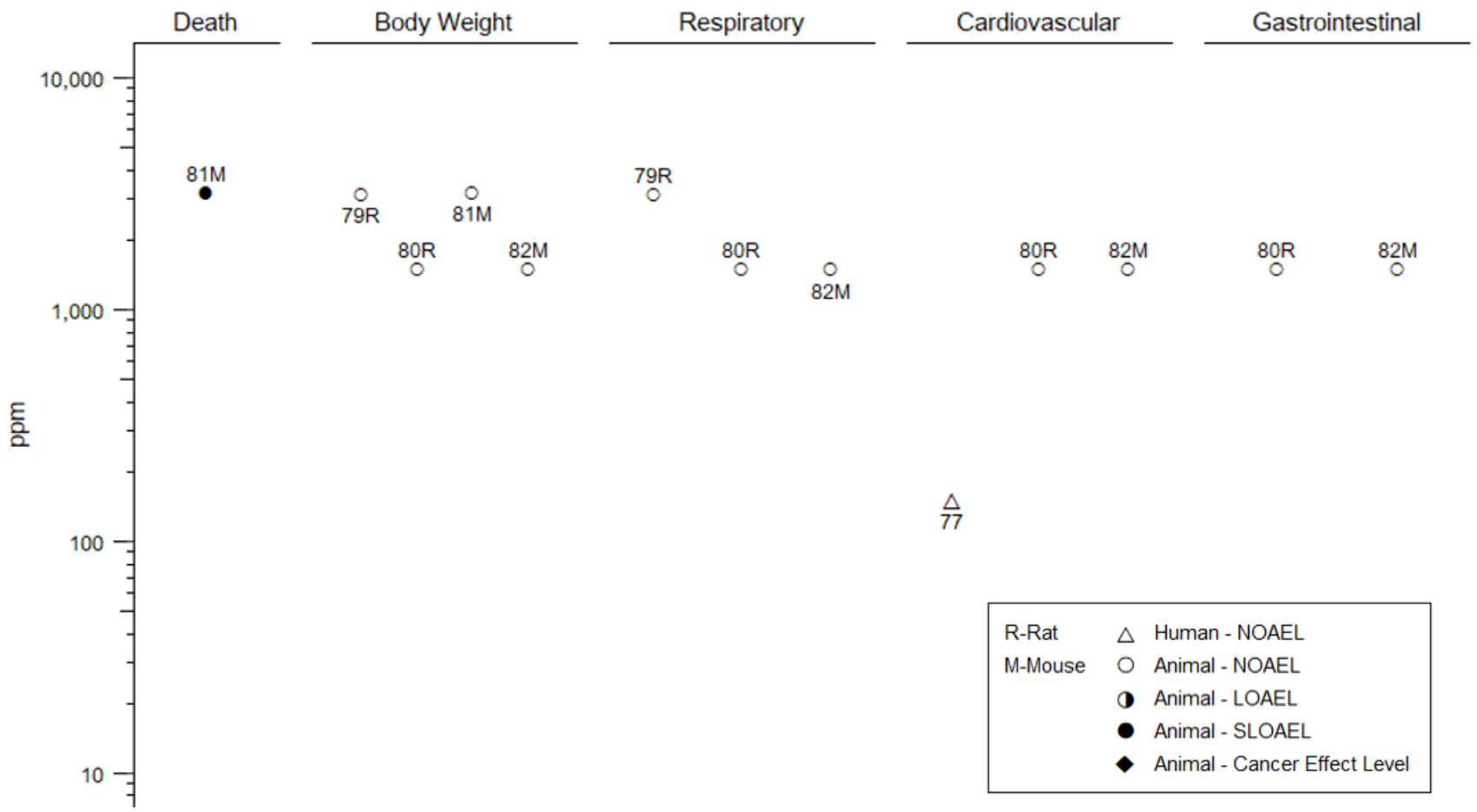


Figure 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation
Chronic (≥365 days)

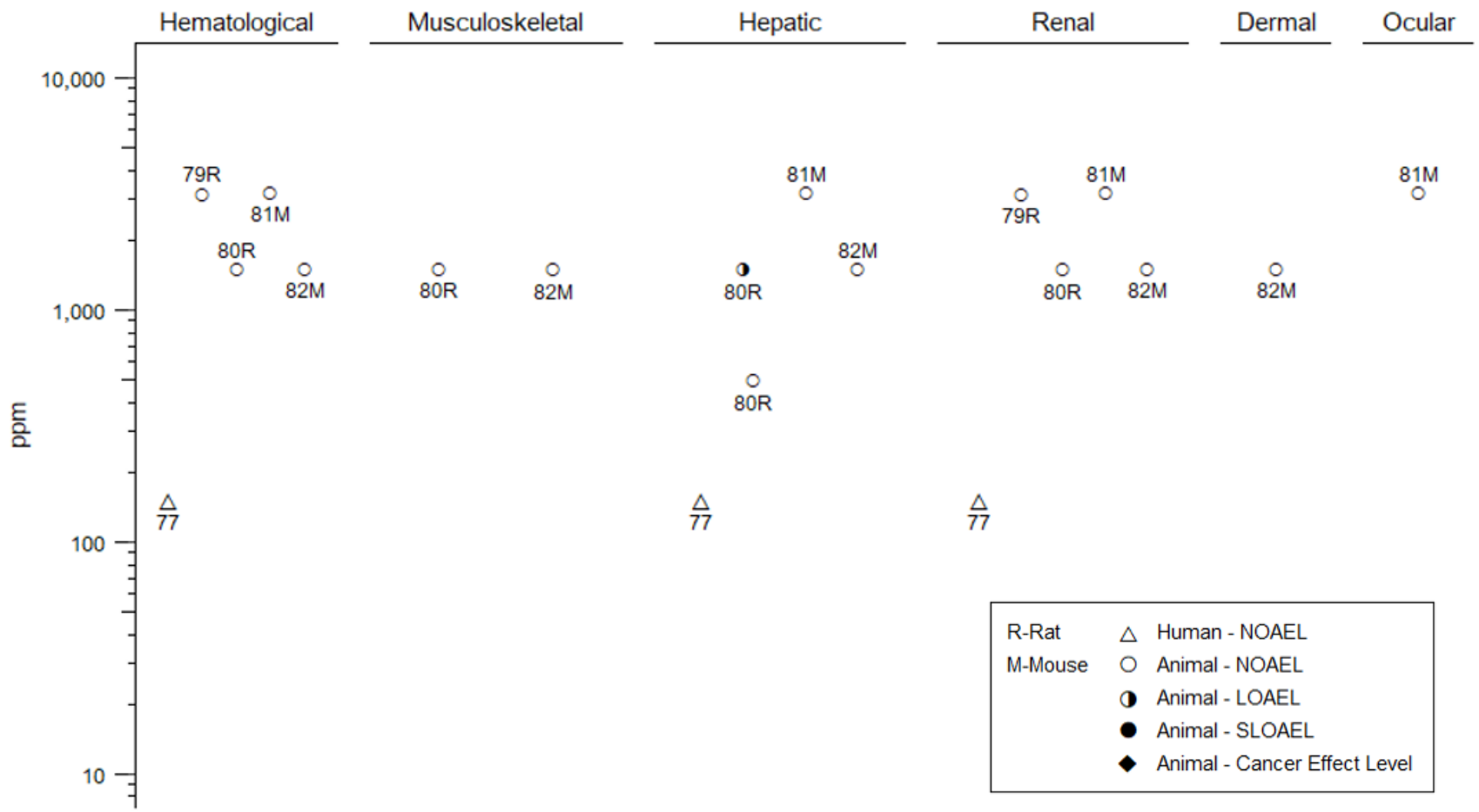


Figure 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation
Chronic (≥365 days)

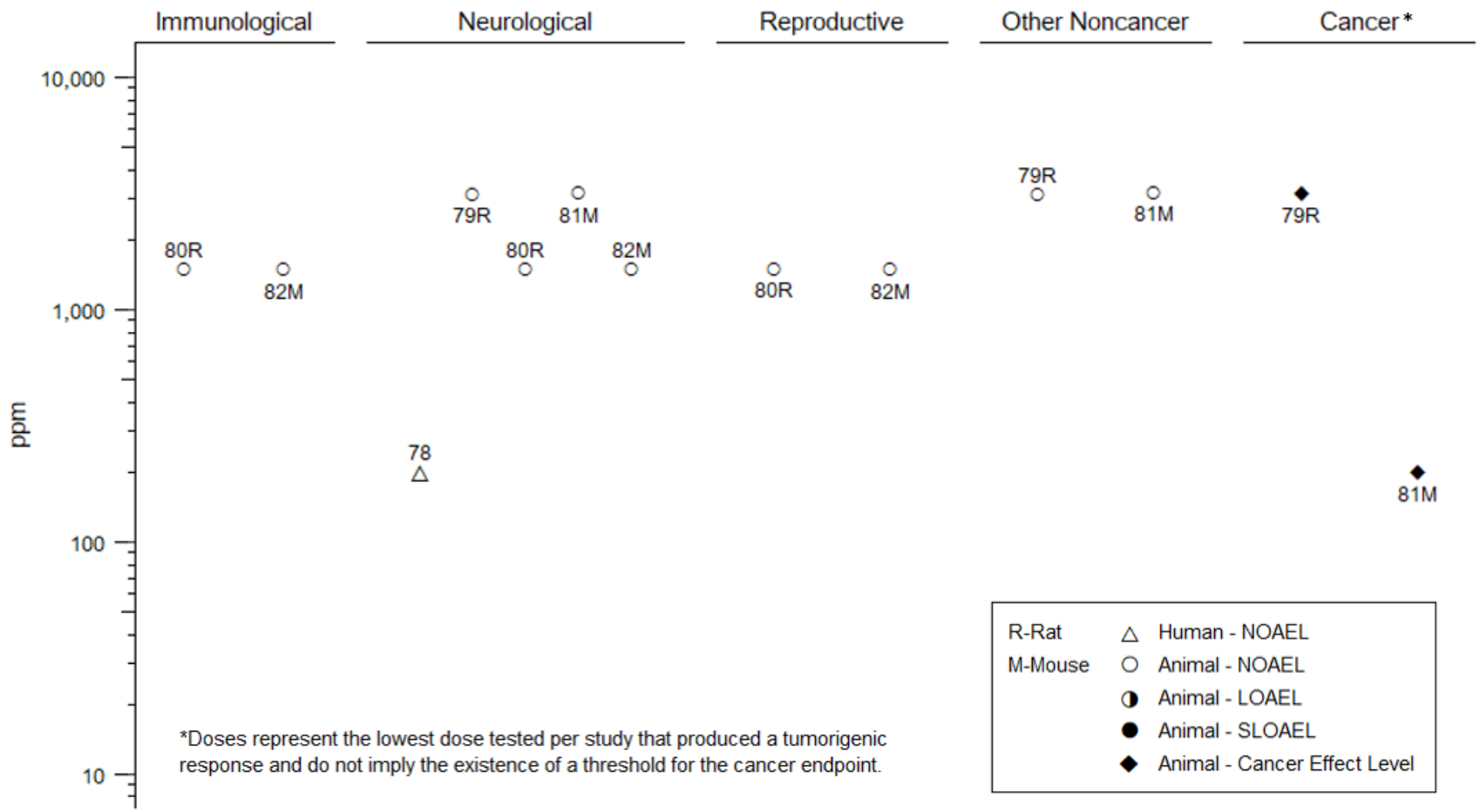


Table 2-3. Levels of Significant Exposure to 1,1,1-Trichloroethane – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
Bruckner et al. 2001									
1	Rat (Sprague-Dawley) 4–6 M	Once (GO)	0, 500, 1,000, 2,000, 4,000	BC, BI, GN, HP, LE, OF	Bd wt	4,000			
					Hepatic	4,000			
					Renal	4,000			
Bruckner et al. 2001									
2	Rat (Sprague-Dawley) 15–20 M	11 days 1 time/day; days 1–5 and days 8–11 (GO)	0, 500, 5,000, 10,000	BC, BI, GN, HP, LE, NX, OW	Death			5,000	3/15 died
					Bd wt	500	5,000		17% decrease in final body weight
					Hepatic	10,000			
					Neuro	500		5,000	Hyperexcitability followed by narcosis
Platt and Cockrill 1969									
3	Rat (NS) 4–5 NS	7 days once/day (GO)	0, 1,650	BI, BW, CS, OW	Bd wt	1,650			
					Hepatic	1,650			
Spencer et al. 1990									
4	Rat (Fischer 344) 11–12 F	4 days once/day (GO)	0, 705	CS, NX	Bd wt	705			
					Neuro		705		Increased latency in FEPs by 5.2 milliseconds; EEG changes (292% decrease in amplitude in the low frequency band)
Torkelson et al. 1958									
5	Mouse (NS) 16 F	Once (G)		CS	Death			11,240	LD_{50}
Torkelson et al. 1958									
6	Guinea pig (NS) 16 M	Once (G)		CS	Death			9,470	LD_{50}

Table 2-3. Levels of Significant Exposure to 1,1,1-Trichloroethane – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
INTERMEDIATE EXPOSURE									
Bruckner et al. 2001									
7	Rat (Sprague-Dawley) 15–20 M	7–13 weeks 5 days/week (GO)	0, 500, 2,500, 5,000	BC, BI, BW, GN, HP, LE, NX, OW	Death			2,500	5/15 rats died
					Bd wt	500		2,500	19% decrease in final body weight
					Resp	500		2,500	Pulmonary congestion in deceased animals
					Hepatic	5,000			
					Renal	5,000			
					Neuro	500		2,500	Hyperexcitability followed by hours of narcosis after daily dosing
Dow Chemical 1993; Maurissen et al. 1994									
8	Rat (Fischer-344 25 F	GDs 6–21 LDs 1–10 (GO)	0, 75, 250, 750	BW, CS, DX, GN, HP, NX, RX	Develop	750			
George et al. 1989									
9	Rat (Sprague-Dawley) 150 M, 150 F	27 days (males and nonbreeding females) *ad libitum*; 70 days pregnant females *ad libitum* (W)	0, 0.3, 0.9, 2.60, M: 0.3, 0.9, 2.6; F (premating): 0.3, 1.3, 3.3; F (gestation): 0.3, 1.2, 3.5 F(postnatal): 0.6, 2.0, 5.9	BW, FI, WI, RX, DX	Bd wt	3.5			
					Repro	3.5 F			
					Develop	5.9			

Table 2-3. Levels of Significant Exposure to 1,1,1-Trichloroethane – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
George et al. 1989; NTP 1988a									
10	Rat (CD) 36 M, 36 F	70 days *ad libitum* (W)	M: 0, 0.3, 0.9, 2.6 F (pre-mating): 0.3, 1.3, 3.3 F (gestation): 0.3, 1.2, 3.5; F (postnatal): 0.6, 2.0, 5.9	BW, CS, DX, FI, OW, RX, WI	Repro Develop	3.3 F 3.5			
NTP 1988b									
11	Rat (Sprague-Dawley) 37 M, 37 F	40 days *ad libitum* (W)	0 M: 0.26, 0.64, 2.0; F (premating): 0.30, 0.79, 2.0; F (gestation): 0.34, 0.84, 2.4	BW, CS, DX, FI, OW, RX, WI	Repro Develop	2 F 2.4 F			
NTP 2000									
12	Rat (F344/N) 10 M, 10 F	13 weeks *ad libitum* (F)	M: 0, 290, 600, 1,200, 2,400, 4,800; F: 0, 310, 650, 1,250, 2,500, 5,000	BC, BW, CS, FI, GN, HE, HP, OW, UR	Bd wt	4,800 F 2,400 M	4,800 M		10% decrease in final body weight
					Hepatic	2,500 F	5,000 F		Decrease in absolute and relative liver weights
						2,400 M	4,800 M		Decrease in absolute liver weights
					Renal	5,000 F 4,800 M			

Table 2-3. Levels of Significant Exposure to 1,1,1-Trichloroethane – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Repro	2,400 M	4,800 M		10% reduction in epididymal spermatozoa concentration
Lane et al. 1982									
13	Mouse (Swiss ICR) 10 M, 30 F	25 weeks *ad libitum* (W)	0, 100, 300, 1,000	BW, CS, DX, GN, RX, WI	Repro	1,000 F			
					Develop	1,000			
NTP 2000									
14	Mouse (B6C3F1) 10 M, 10 F	13 weeks *ad libitum* (F)	M: 0, 850, 1,750, 3,500, 7,370, 15,000; F: 0, 1,340, 2,820, 5,600, 11,125, 22,900	BC, BW, CS, FI, GN, HE, HP, LE, OW, UR	Bd wt	2,820 F	850 M[b]	5,600 F	LOAEL: 9% decrease in final body weight; 18% decrease in body weight gain $BMDL_{10}$ = 208 mg/kg/day SLOAEL: 11% decreased final body weight; 33% decreased body weight gain
					Cardio	22,900 F			
						15,000 M			
					Hepatic	22,900 F			
						15,000 M			
					Renal	22,900 F			
						15,000 M			
					Repro	22,900 F			
						15,000 M			

Table 2-3. Levels of Significant Exposure to 1,1,1-Trichloroethane – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
CHRONIC EXPOSURE									
Maltoni et al. 1986									
15	Rat (Sprague-Dawley) 40 M, 40 F	104 weeks 4–5 days/week (GO)	0, 500	GN, HP, BW	Bd wt		500 F		12% decrease in final body weight
					Cancer			500	CEL: Leukemia (total leukemias in 9/40 males, 4/40 females and 13/80 combined)
NCI 1977									
16	Rat (Osborne-Mendel) 50 M, 50 F	78 weeks 5 days/week (GO)	0, 750, 1,500	BW, FI, GN, HP, CS	Death			750	41/50 females died. 49/50 males died
					Bd wt	1,500			
					Resp	1,500			
					Cardio	1,500			
					Gastro	1,500			
					Hemato	1,500			
					Musc/skel	1,500			
					Hepatic	1,500			
					Renal	1,500			
					Dermal	1,500			
					Immuno	1,500			
					Neuro	1,500			
					Repro	1,500			
NCI 1977									
17	Mouse (B6C3F1) 50 M, 50 F	78 weeks 5 days/week (GO)	0, 2,807, 5,615	GN, HP, BW, CS	Death			2,807	22/50 females died: 29/50 males died
					Bd wt		2,807		~18% decrease in final body weight for males; ~10% decrease in final body weight for females

Table 2-3. Levels of Significant Exposure to 1,1,1-Trichloroethane – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Resp	5,615			
					Cardio	5,615			
					Gastro	5,615			
					Hemato	5,615			
					Musc/skel	5,615			
					Hepatic	5,615			
					Renal	5,615			
					Dermal	5,615			
					Immuno	5,615			
					Neuro	5,615			
					Repro	5,615			

[a]The number corresponds to entries in Figure 2-3; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-3. Where such differences exist, only the levels of effect for the most sensitive sex are presented.
[b]Used to derive an intermediate-duration oral MRL of 2 mg/kg/day based on decreased body weight. See Appendix A for more detailed information regarding the MRL.

BI = biochemical changes; BC = blood chemistry; Bd wt or BW = body weight; $BMDL_{10}$ = benchmark dose lower confidence limit 10%; Cardio = cardiovascular; CEL = cancer effect level; CS = clinical signs; Develop = developmental; DX = developmental toxicity; EEG = electroencephalograph; (F) = food F = female(s); FEP = flashed evoked potential; FI = food intake; (G) = gavage; Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; (GO) = gavage in oil; HE = hematology; Hemato = hematological; HP = histopathological; Immuno = immunological; LD = lactation day; LD_{50} = median lethal dose; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); MRL = Minimal Risk Level; Musc/skel = musculoskeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; NX = neurological function; OF = organ function; OW = organ weight; Repro = reproductive; Resp = respiratory; RX = reproductive toxicity; SLOAEL = serious LOAEL; UR = urinalysis; (W) = water; WI = water intake

Figure 2-3. Levels of Significant Exposure to 1,1,1-Trichloroethane – Oral
Acute (≤14 days)

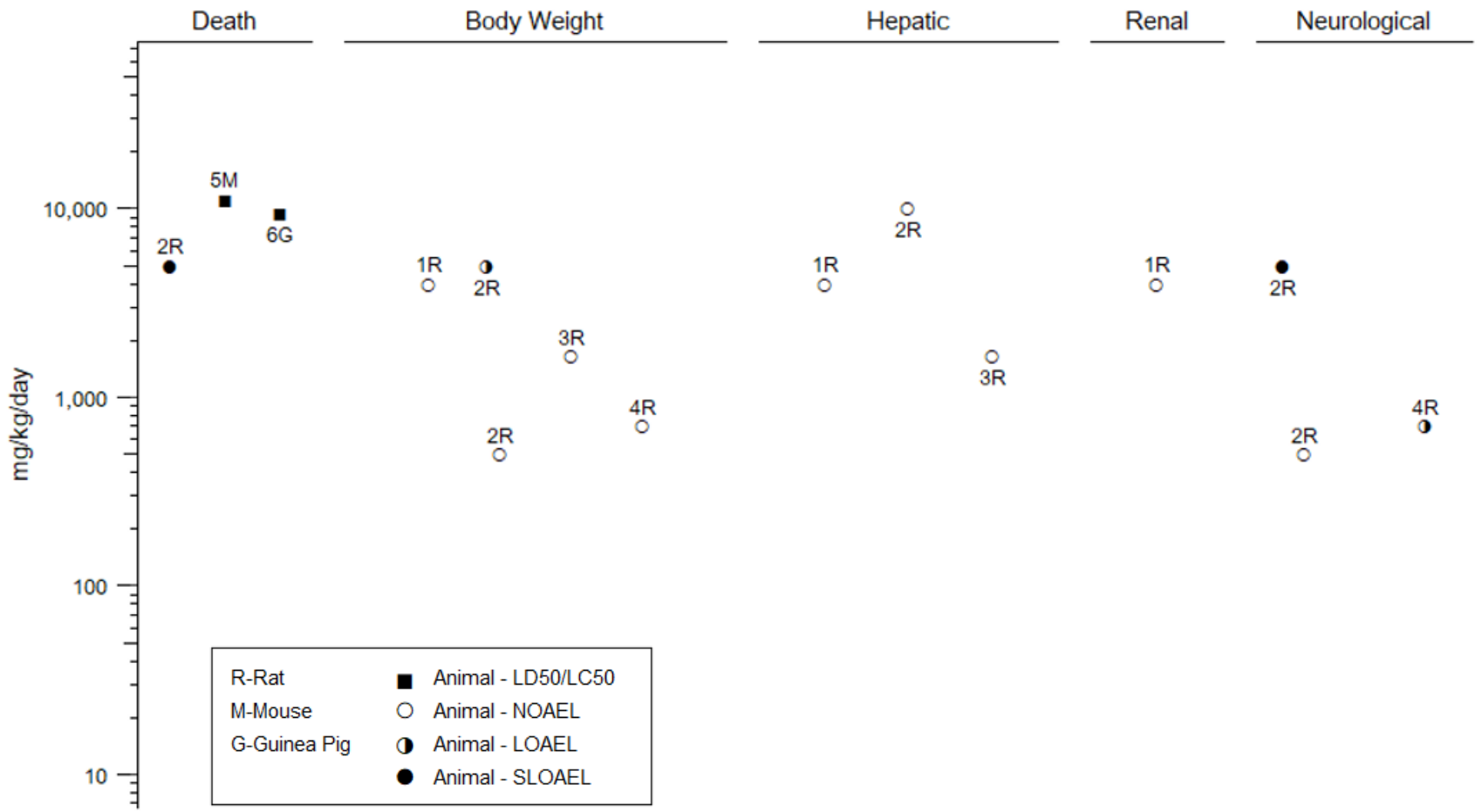


Figure 2-3. Levels of Significant Exposure to 1,1,1-Trichloroethane – Oral
Intermediate (15–364 days)

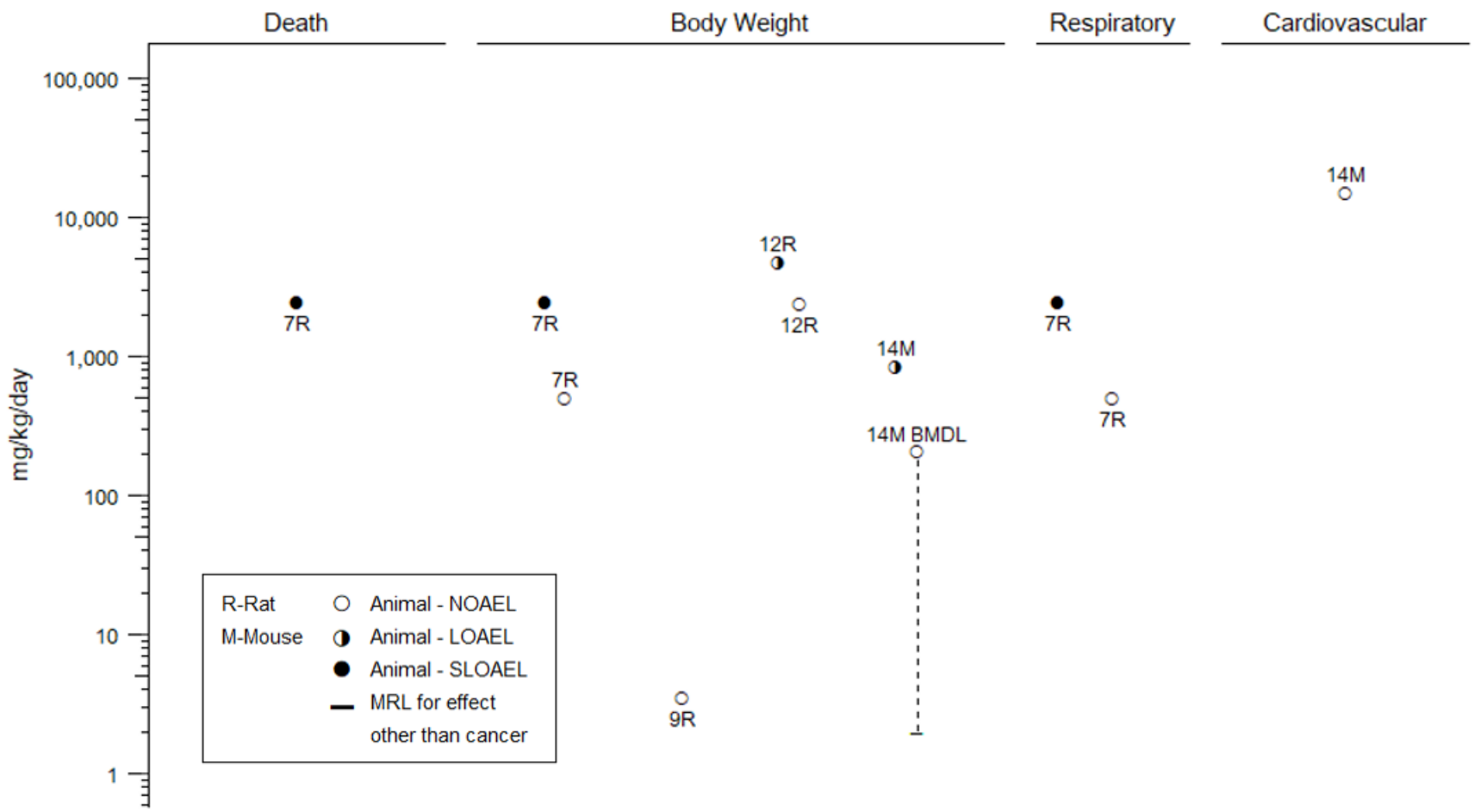


Figure 2-3. Levels of Significant Exposure to 1,1,1-Trichloroethane – Oral
Intermediate (15–364 days)

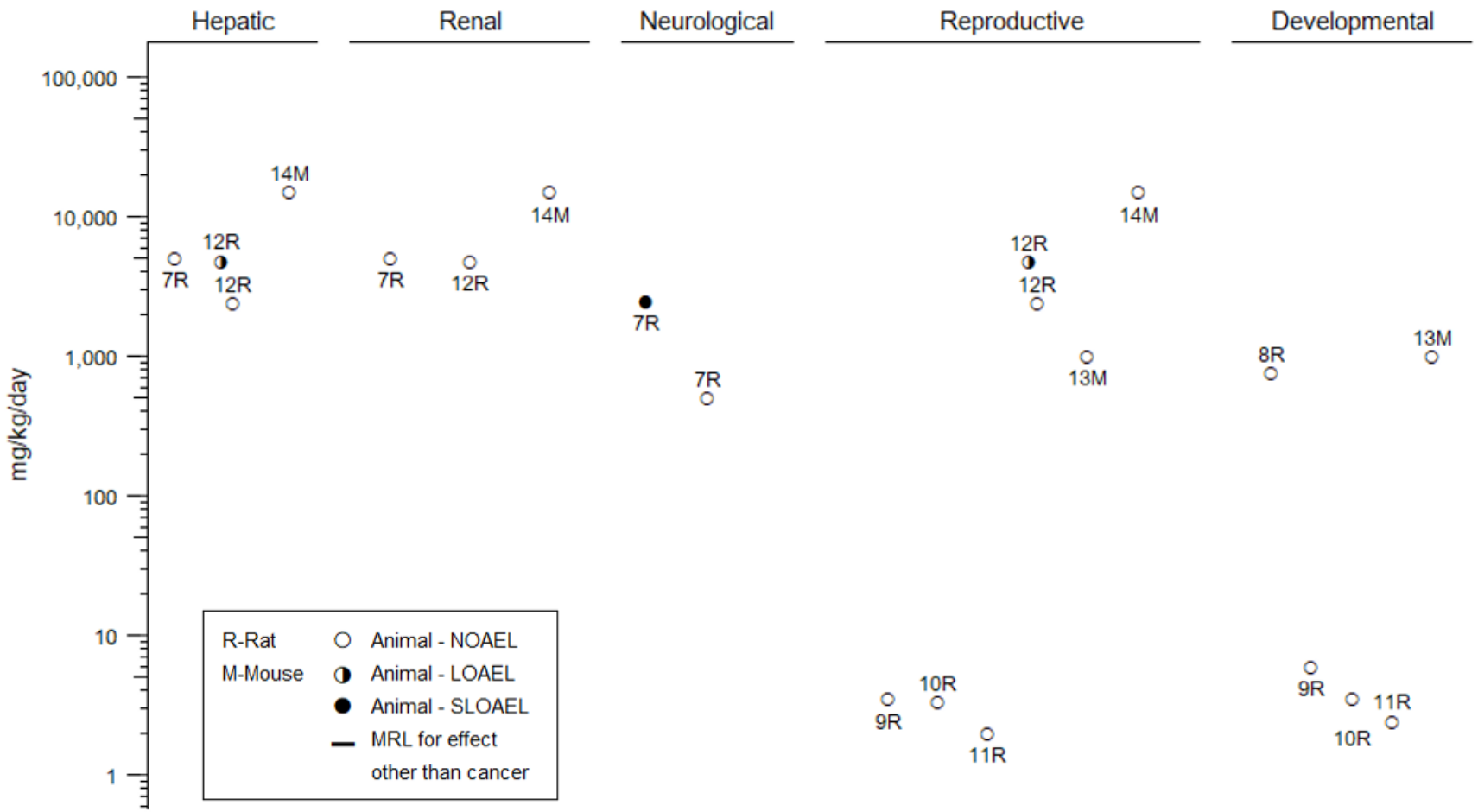


Figure 2-3. Levels of Significant Exposure to 1,1,1-Trichloroethane – Oral
Chronic (≥365 days)

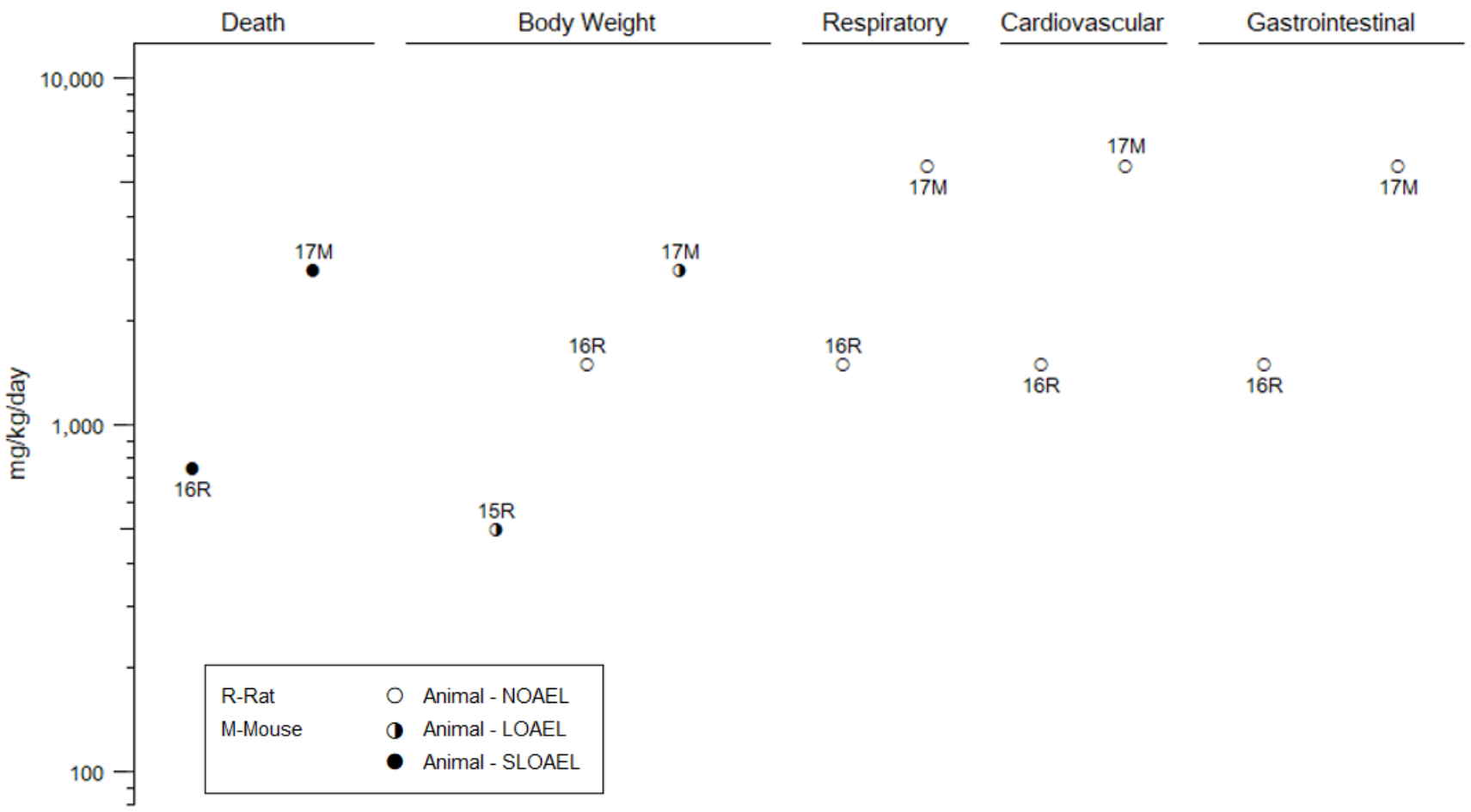


Figure 2-3. Levels of Significant Exposure to 1,1,1-Trichloroethane – Oral
Chronic (≥365 days)

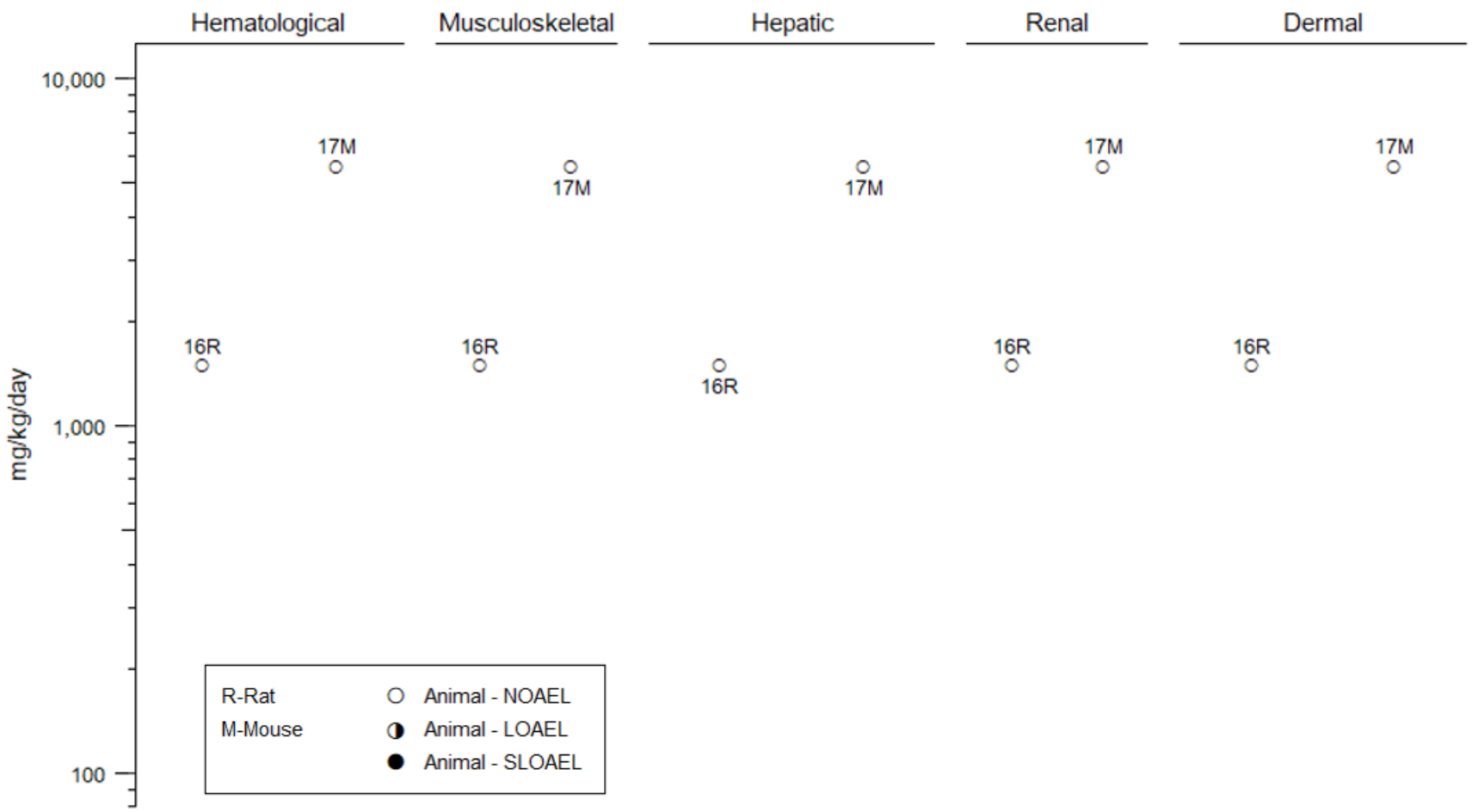


Figure 2-3. Levels of Significant Exposure to 1,1,1-Trichloroethane – Oral
Chronic (≥365 days)

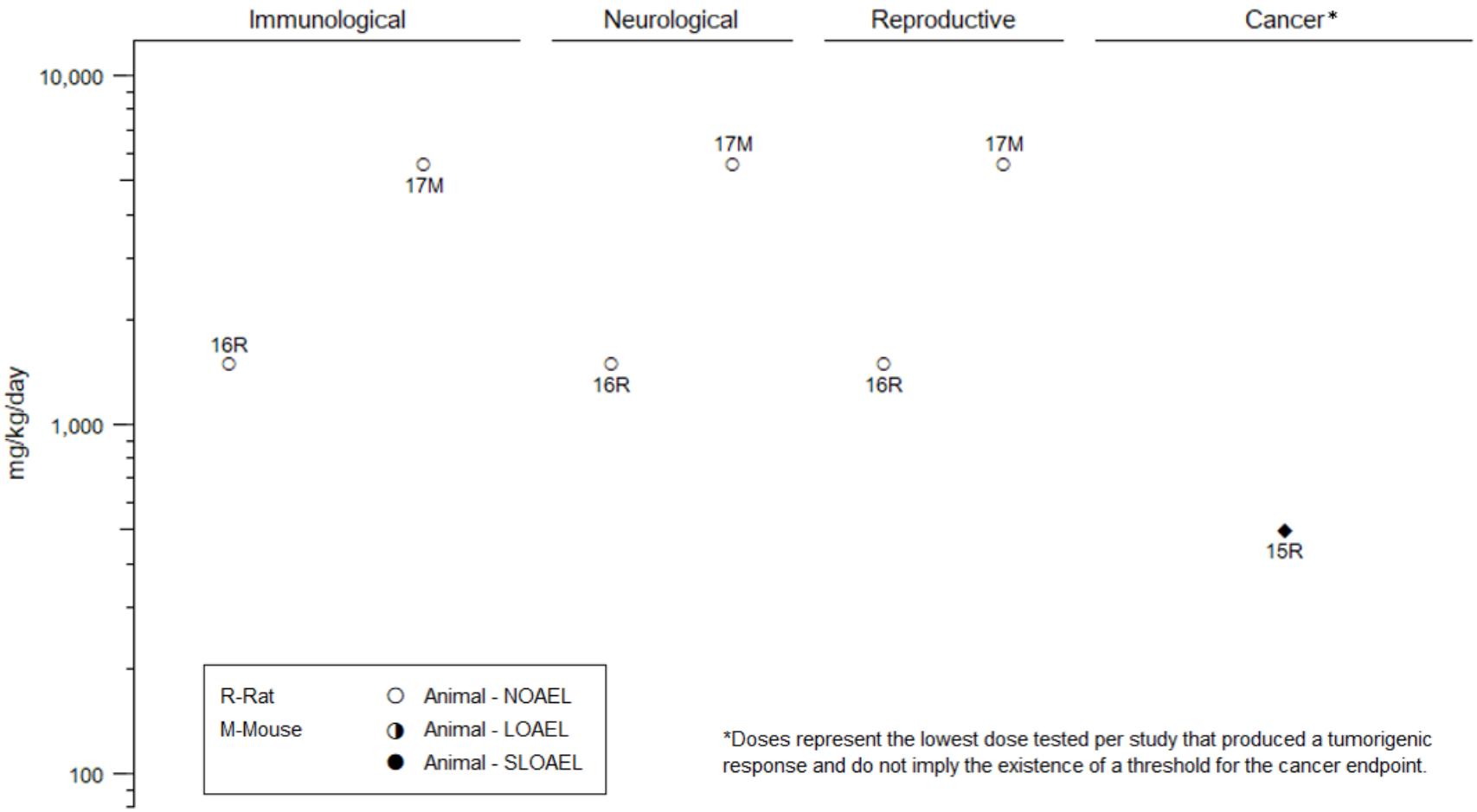


Table 2-4. Levels of Significant Exposure to 1,1,1-Trichloroethane – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE								
Marzulli and Ruggles 1973								
Rabbit (NS) 6 B	Once	50	GN, HP, CS	Ocular	50			
INTERMEDIATE EXPOSURE								
Viola et al. 1981								
Rat (Wistar) 8–10 M	22 days: 8 days once/day, 6 days 0/day, 8 days once/day	0, 280	BC, BW, HP, UR	Bd wt			280	60% decrease in body weight gain
				Gastro	280			
				Hepatic		280		Hepatocellular alterations that included small focal intralobular inflammatory infiltrates; within the hepatocytes, swollen mitochondria and microvacuoles of fatty degeneration; disruption in other cytoplasmic organelles: 650% increase in CPK, 260% increase in OCT, 80% increase in GGT
				Renal	280			
Torkelson et al. 1958								
Rabbit (Albino) 4 M	90 days 5 days/week	0, 15, 50, 100, 200, 500	BC, BW, CS, FI, GN, HP, OW	Bd wt	500			
				Resp	500			
				Cardio	500			
				Gastro	500			
				Hemato	500			
				Hepatic	500			
				Renal	500			
				Dermal		15		Mild skin irritation (not otherwise described)
				Immuno	500			

Table 2-4. Levels of Significant Exposure to 1,1,1-Trichloroethane – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
				Neuro	500			
				Repro	500			

B = both males and females; BC = blood chemistry; Bd wt or BW = body weight; Cardio = cardiovascular; CPK = creatine phosphokinase; CS = clinical signs; FI = food intake; Gastro = gastrointestinal; GGT = gamma-glutamyl transferase; GN = gross necropsy; Hemato = hematological; HP = histopathological; Immuno = immunological; LOAEL = lowest-observed-adverse-effect level; M = male(s); Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OCT = organic cation transporter; OW = organ weight; Repro = reproductive; Resp = respiratory; UR = urinalysis

2.2 DEATH

Lethal effects of 1,1,1-trichloroethane were seen in case studies where individuals were exposed to 1,1,1-trichloroethane through inhalation (Jones and Winter 1983; Northfield 1981; Silverstein 1983). Simulation of the circumstances of deaths in two people exposed while using 1,1,1-trichloroethane as a solvent, showed that concentrations up to 6,410 ppm may have been generated in one case (Jones and Winter 1983), and a concentration of 9,000 ppm was estimated in the other (Silverstein 1983). Northfield (1981) reported a case in which a worker, whose death was attributed to respiratory failure, may have been exposed to 1,1,1-trichloroethane concentrations of 6,000 ppm or higher, depending on distance from the source.

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

In mice, reported LC_{50} values ranged from 3,911 to 22,241 ppm, with higher values associated with shorter exposure durations (Gradiski et al. 1978; Horiguchi and Horiuchi 1971; Moser and Balster 1985; Woolverton and Balster 1981). For example, Moser and Balster (1985) reported LC_{50} values of 29,492, 20,616, and 18,358 ppm for 10-, 30-, and 60-minute exposures, respectively. Clark and Tinston (1982) reported an LC_{50} of 38,000 ppm in rats following a 15-minute exposure. Gehring (1968) reported an LT_{50} of 595 minutes following exposure to 1,1,1-trichloroethane at a concentration of 13,500 ppm. Two out of six male rats died after exposure to 11,550 ppm for up to 4 hours (Mullin and Krivanek 1982).

Mortality was not reported in intermediate-duration studies where exposure was up to 5,000 ppm (Prendergast et al. 1967; Rosengren et al. 1985) or in a chronic-duration study where exposures were up to 1,750 ppm (Quast et al. 1988). There were no significant differences in the survival rates of F344 rats

of both sexes after exposure to concentrations up to 3,181 ppm for 6 hours/day, 5 days/week, for 104 weeks (Ohnishi et al. 2013). In the same study, decreased survival rates were observed in male BDF1 mice exposed to 3,204 ppm; however, there were no dose-related differences in survival in female BDF1 mice at concentrations up to 3,204 ppm with the same exposure schedule.

No studies were identified regarding the lethal effects in humans after oral exposure to 1,1,1-trichloroethane.

Kinkead and Wolfe (1992) reported oral LD_{50} values of 17,148 and 12,996 mg/kg for male and female mice, respectively, after acute-duration exposures to 1,1,1-trichloroethane. In an earlier study, Torkelson et al. (1958) reported acute oral LD_{50} values in several animal species: 12,300 and 10,300 mg/kg for male and female rats, 11,240 mg/kg for mice, 9,470 mg/kg for guinea pigs, and 5,660 mg/kg for rabbits. Three of 15 Sprague-Dawley rats died after oral exposure to 5,000 mg/kg/day for 11 days (Bruckner et al. 2001). Gavage doses of 5,620 mg/kg/day in Osborne-Mendel rats and 10,000 mg/kg/day in B6C3F1 mice for 6 weeks resulted in lethality in 2/10 rats and 8/10 mice (NCI 1977). However, survival rates were not affected by dietary exposure to doses as high as 5,000 mg/kg/day in F344/N rats and 23,000 mg/kg/day in B6C3F1 mice for 13 weeks (NTP 2000). Oral exposure to 2,500 mg/kg/day for 5 days/week for 51 days resulted in death in 5/15 Sprague-Dawley rats (Bruckner et al. 2001). It is worth noting that the Bruckner et al. (2001) study mentioned that surviving rats of the 2,500 and 5,000 mg/kg/day groups were mistakenly killed on day 51 of the 13-week study. There was no effect on mortality in the control or 500 mg/kg/day group that continued for the full 13 weeks. Decreased survival was observed in Osborne-Mendel rats exposed to 750 mg/kg/day by gavage and B6C3F1 mice exposed to 2,807 mg/kg/day in a chronic-duration study (NCI 1977). Chronic-duration exposure to 500 mg/kg/day by gavage did not have any impact on survival rates in Sprague-Dawley rats (Maltoni et al. 1986).

No studies were identified regarding the lethal effects in humans after dermal exposure to 1,1,1-trichloroethane.

A 24-hour application 15,800 mg/kg/day of 1,1,1-trichloroethane to the skin of rabbits resulted in <50% mortality of eight rabbits (incidence not reported), whereas a lower dose of 3,980 mg/kg/day had no effect on mortality (Torkelson et al. 1958). No mortality was noted in rabbits exposed to 2 mL/kg for 24 hours or guinea pigs exposed to 2 mL for 35 days (AAMRL 1987; Wahlberg and Boman 1979). Mortality rates in rats and rabbits were not affected by intermediate-duration dermal application of doses up to 280 mg/kg/day (covered) or 500 mg/kg/day (uncovered) (Torkelson et al. 1958).

2.3 BODY WEIGHT

No inhalation studies were identified that investigated body weight changes in humans, but studies in several animal species consistently showed decreased mean body weight.

Several acute-duration studies reported no effects on final body weight up to 8,000 ppm in mice (Calhoun et al. 1981; Jones et al. 1996; Schwetz et al. 1975), up to 18,000 ppm in rats (Adams et al. 1950; BRRC 1987b; Calhoun et al. 1981; Cornish and Adefuin 1966), or up to 6,000 ppm in rabbits (BRRC 1987a). In mice, continuous exposures to a concentration of 4,000 ppm over 4 days caused a 25% reduction in mean body weight measured 96 hours after exposure (Evans and Balster 1993). Despite having no effects on final body weights, animals in these studies sometimes exhibited a decrease in body weight gain.

Body weight remained unaffected in most intermediate-duration studies across animal species at concentrations up to 2,210 ppm as shown in Table 2-2. In multiple studies, Adams et al. (1950) exposed guinea pigs to different concentrations of 1,1,1-trichloroethane for 7 hours/day, 5 days/week for multiple intermediate durations resulting in decreased final body weights for the following exposures: 3,000 ppm exposure for 29 days (12–13% decrease); 5,000 ppm for 45 days (10–11% decrease); 650 ppm for 58 days (11% decrease in females, but not males); and 650 ppm for 93 days (10% decrease in males, but not females). However, exposure of guinea pigs to 1,500 ppm for 60 days had no effect on final body weights. These studies showed decreases in body weight gains ranging from 17 to 53% over the course of the study, which is commonly seen when there is an initial, transient decrease in food consumption correlating with the start of exposure. There were no significant differences in terminal body weight between any of the 1,1,1-trichloroethane-exposed groups and the controls in either male or female F344 rats exposed to concentrations up to 3,181 ppm, or in BDF1 mice exposed to concentrations up to 3,204 ppm for 6 hours/day, 5 days/week, for 104 weeks (Ohnishi et al. 2013).

No oral studies were identified that investigated body weight changes in humans, but studies in multiple animal species showed decreased final body weight.

There were no effects on mean body weights in acute-duration oral studies up to 5,000 mg/kg/day in rats (Bruckner et al. 2001; Platt and Cockrill 1969; Spencer et al. 1990). Acute-duration, 11-day oral exposure to 5,000 mg/kg/day of 1,1,1-trichloroethane caused a 17% decrease in final body weights in Sprague-Dawley rats (Bruckner et al. 2001).

Intermediate- and chronic-duration oral studies in animals show adverse effects of exposure to 1,1,1-trichloroethane on body weight. A decrease of final body weights by 19% was seen after oral exposure to 2,500 mg/kg/day for 13 weeks (5 days/week) (Bruckner et al. 2001). In a 13-week study, NTP (2000) reported reductions in final body weight and body weight gain in rats and mice of both sexes exposed to microencapsulated 1,1,1-trichloroethane in feed. Final body weight was reduced by 10% in male rats exposed to 4,800 mg/kg/day compared to the vehicle controls. Female rats exposed to 5,000 mg/kg/day had no change in body weight. There was no difference in body weights when compared to untreated controls. In male and female mice, a 10–11% reduction in final body weight occurred at doses of 3,500 and 5,600 mg/kg/day, respectively (NTP 2000). No effects on final body weights were reported in a 78-week study in rats exposed to 1,500 mg/kg/day or mice exposed to 5,615 mg/kg/day (NCI 1977). This study reported that the body weight gain was reduced; however, the size of reduction was not quantified and in the absence of changes reflected in final body weights, it is of unclear significance (NCI 1977). A 12% reduction in final body weight occurred in female rats, but not in male rats, exposed to 500 mg/kg/day of 1,1,1-trichloroethane over 104 weeks (Maltoni et al. 1986).

No dermal studies were identified that investigated body weights in humans after exposure to 1,1,1-trichloroethane.

Four studies examined the effects of dermal exposure to 1,1,1-trichloroethane on body weight in animals; however, none of these studies reported food consumption, possibly confounding the occurrence or magnitude of body weight reduction due to 1,1,1-trichloroethane exposure. In an acute-duration study in guinea pigs, no effects on mean body weights were observed through day 35 following dermal exposure to 7,360 mg/kg for 5–7 days (Wahlberg and Boman 1979). Additionally, no effect on mean body weight was reported in rabbits exposed to a dose of 2,680 mg/kg for 24 hours 14 days after exposure (AAMRL 1987). In an intermediate-duration study where 1,1,1-trichloroethane was applied to the skin of rats for 8 days, then 6 days untreated, followed by a second 8-day exposure at doses ranging from 240 to 320 mg/kg (middle of range: 280 mg/kg), a 10% reduced final body weight was reported, with a 60% decrease in body weight gain (Viola et al. 1981). Torkelson et al. (1958) applied 1,1,1-trichloroethane to the uncovered skin of rabbits at doses up to 500 mg/kg for 90 days with no apparent effect on mean body weight.

2.4 RESPIRATORY

Little information on acute-duration exposure of humans to inhaled 1,1,1-trichloroethane is available. In humans, acute-duration exposure to high concentrations of 1,1,1-trichloroethane can produce respiratory depression (Kelly and Ruffing 1993), leading to death (Hall and Hine 1966; Jones and Winter 1983; Stahl et al. 1969; Winek et al. 1997). Six out of seven men exposed to 2,650 ppm (progressive exposure from 0 to 2,650 ppm) for up to 186 minutes reported throat irritation (self-reported) (Stewart et al. 1961). Respiratory inflammation indicated by increased concentrations of proinflammatory cytokines was reported in 12 male subjects following exposure to 200 ppm 1,1,1-trichloroethane for 4 hours (Muttray et al. 1999).

Respiratory failure as a cause of death has been reported in several species of animals acutely exposed to high 1,1,1-trichloroethane concentrations (248–657 mg/kg) (Krantz et al. 1959). Respiratory distress was reported in rats exposed to 6,100 ppm for up to 4 hours (Mullin and Krivanek 1982). However, no histopathological changes were reported in the lungs after acute-duration exposures up to 15,000 ppm in rats or 25,000 ppm in dogs (Cornish and Adefuin 1966; Herd et al. 1974).

Torkelson et al. (1958) reported lung irritation and inflammation in Guinea pigs exposed to 1,000 ppm for 3 months. Degenerative changes in the olfactory epithelium of the nasal turbinates were present in 10/10 male and 10/10 female CDF rats after a 13-week (5 days/week, 6 hours/day) exposure to 1,976 ppm 1,1,1-trichloroethane (Calhoun et al. 1981). However, some intermediate-duration exposures did not produce any histopathological changes in mice, rats, guinea pigs, rabbits, dogs, or monkeys at exposures up to 2,210 ppm (MacEwen and Vernot 1974; Prendergast et al. 1967; Torkelson et al. 1958; Truffert et al. 1977). No histopathological changes were reported in rats and mice exposed to concentrations up to 3,204 ppm for 2 years (Ohnishi et al. 2013; Quast et al. 1988).

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

There were no acute-duration oral studies found that identified adverse respiratory effects. Oral exposure to 2,500 mg/kg/day for 13 weeks (5 days/week) in water resulted in pulmonary congestion as the cause of death in Sprague-Dawley rats (Bruckner et al. 2001). There were no lesions observed in the lungs, trachea, or nasal passages of mice and rats exposed to 1,1,1-trichloroethane by gavage at doses up to 5,615 mg/kg/day (mice) or 1,500 mg/kg/day (rats) for 78 weeks (NCI 1977).

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

Dermal exposure to 500 mg/kg/day of 1,1,1-trichloroethane (uncovered) for 90 days had no effect on lung weight or gross or microscopic lung lesions in rabbits (Torkelson et al. 1958).

2.5 CARDIOVASCULAR

Acute-duration exposure to a lower concentration (506 ppm for 450 minutes or 566 ppm for four exposures of 30 minutes) of 1,1,1-trichloroethane did not affect clinical cardiovascular parameters such as blood pressure or pulse rate in the humans tested (Gamberale and Hultengren 1973; Torkelson et al. 1958).

In a matched pair epidemiological study, workers exposed to 1,1,1-trichloroethane at concentrations <250 ppm over 6 years had no differences in blood pressure, heart rate, or electrocardiogram compared to the unexposed group (Kramer et al. 1978). When estimating a regression of the cumulative dose, there was a positive association between 1,1,1-trichloroethane exposure and P-wave duration. In a matched-pair analysis of 151 textile workers, cumulative dose exposure to 1,1,1-trichloroethane (stratified by quintiles: 1–14, 15–49, 50–99, 100–149, and 150–249 ppm) estimated by job exposure index and body burden (measured by breath analysis) was positively correlated with P-wave duration as a cardiac outcome, although correlation was unquantified (Kramer et al. 1978).

Acute-duration exposure to 1,1,1-trichloroethane at concentrations of ≥5,000 ppm produced sensitization of the heart to epinephrine-induced arrhythmias in both rabbits and dogs (Carlson 1981; Clark and Tinston 1973; Reinhardt et al. 1973). The arrhythmias occurred after only a few minutes of exposure, and they quickly disappeared after the end of exposure. In rabbits, there was evidence that susceptibility to arrhythmia increased with exposure duration, and that 1,1,1-trichloroethane itself, not its metabolites, produced the sensitizing effect (Carlson 1981). Mean arterial blood pressure was reduced by 29% (41 mmHg) in rats exposed to 8,000 ppm for up to 60 minutes (Folbergrova et al. 1984). Herd et al. (1974) reported that mean blood pressure decreased by up to 50 mmHg in dogs exposed to 8,000–25,000 ppm 1,1,1-trichloroethane beginning within 15 seconds of the start of exposure and becoming more pronounced as exposure continued for 5 minutes. Decreased mean blood pressure at both 8,000 and 15,000 ppm (change not reported) was due to a decrease in total peripheral resistance; in addition, an

increase in myocardial contractility and cardiac output was observed. The decrease in blood pressure at 20,000 and 25,000 ppm was caused by reductions in myocardial contractility and cardiac output. Blood pressure returned to pre-exposure values within 15 minutes after termination of exposure, but indices of cardiac output and contractility required 45 minutes to recover. No histopathological changes in the heart were found upon necropsy (Herd et al. 1974).

There were no reported cardiovascular lesions in several animal species (monkeys, rats, mice, guinea pigs) following exposures to concentrations up to 5,000 ppm 1,1,1-trichloroethane for up to 6 months (Adams et al. 1950; Calhoun et al. 1981; Prendergast et al. 1967; Torkelson et al. 1958). Chronic-duration inhalation of up to 2,000 ppm 1,1,1-trichloroethane did not produce cardiovascular lesions in rats or mice (Quast et al. 1988).

No cardiovascular effects were reported in a man who accidently ingested an estimated 600 mg/kg of 1,1,1-trichloroethane in a single dose (Stewart and Andrews 1966).

No cardiovascular lesions were observed in mice exposed to up to 22,900 mg/kg/day or rats exposed to up to 5,000 mg/kg/day in a 13-week repeated-dose study (NTP 2000). In a 78-week oral study, exposure of rats to 1,500 mg/kg/day and mice to 5,615 mg/kg/day did not affect the incidence of cardiac lesions (NCI 1977).

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

Torkelson et al. (1958) conducted a 90-day dermal study in rabbits where exposure to 1,1,1-trichloro-ethane in doses up to 500 mg/kg/day resulted in no changes to heart weight or incidence of heart lesions at any dose level.

2.6 GASTROINTESTINAL

Nausea, vomiting, and diarrhea have been reported in humans exposed to high 1,1,1-trichloroethane concentrations by inhalation (Jones and Winter 1983; McCarthy and Jones 1983; Stewart 1971).

In animals, no gastrointestinal lesions were observed among rats, mice, guinea pigs, or dogs exposed to concentrations as high as 5,615 ppm 1,1,1-trichloroethane for intermediate (Calhoun et al. 1981; MacEwen and Vernot 1974; Torkelson et al. 1958) or chronic durations (Quast et al. 1988).

Vomiting and diarrhea were reported in a man who accidently ingested an estimated 600 mg/kg of 1,1,1-trichloroethane in a single dose (Stewart 1971). Vomiting ensued approximately 1 hour after ingestion with severe and incapacitating diarrhea approximately 2.5 hours after ingestion, with both continuing for 6 hours.

In oral studies, gastrointestinal endpoints examined in animals were limited to histology. In chronic-duration studies, exposures in mice to up to 5,615 ppm and rats to up to 1,500 ppm resulted in no histopathological lesions (NCI 1977).

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

There were no gastrointestinal effects observed in animals dermally exposed to 1,1,1-trichloroethane. Histopathological examination and serum lipase and amylase levels indicated no gastrointestinal or pancreatic damage in rats dermally exposed to 280 mg/kg/day of 1,1,1-trichloroethane under an occlusive dressing for 3 weeks (Viola et al. 1981). Rabbits exposed dermally to 500 mg/kg/day without occlusion for 90 days had no gross or microscopic lesions in the stomach or intestines (Torkelson et al. 1958).

2.7 HEMATOLOGICAL

No evidence was identified that 1,1,1-trichloroethane produces hematological effects in humans after inhalation exposure. Acute-duration inhalation exposures to 1,1,1-trichloroethane at 920 ppm did not adversely affect red or white blood cell counts or hemoglobin levels in humans (Torkelson et al. 1958). In a matched-pair occupational study in textile workers, chronic-duration exposure to up to 249 ppm 1,1,1-trichloroethane did not affect hematological parameters (red blood cells, white blood cells, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and mean corpuscular volume) (Kramer et al. 1978).

No adverse effects were reported for hematological parameters in animals exposed to moderate to high levels of 1,1,1-trichloroethane for any duration (acute, intermediate, or chronic) (Horiguchi and Horiuchi

1971; Koizumi et al. 1983; MacEwen and Vernot 1974; Ohnishi et al. 2013; Prendergast et al. 1967; Quast et al. 1988; Torkelson et al. 1958; Truffert et al. 1977). No consistent changes in hematological parameters were observed in rats exposed to concentrations of 1,1,1-trichloroethane up to 1,976 ppm for 85 days (Calhoun et al. 1981).

No adverse effects were observed on hematological parameters in a man 4 hours after accidentally drinking a single 600 mg/kg dose of 1,1,1-trichloroethane (Stewart and Andrews 1966).

No hematological effects were reported following a 13-week oral exposure to 1,1,1-trichloroethane in the diet at doses up to 5,000 mg/kg/day in rats or 22,900 mg/kg/day in mice (NTP 2000). Chronic-duration gavage exposure to 1,1,1-trichloroethane at doses of 1,500 mg/kg/day in rats and 5,615 mg/kg/day in mice did not affect the incidence of non-neoplastic lesions in bone marrow (NCI 1977), relative to control.

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

In rabbits, hematological parameters, including red blood cell count, white blood cell count, and hemoglobin were unaffected by dermal exposure to 500 mg/kg/day of 1,1,1-trichloroethane (uncovered) for 90 days (Torkelson et al. 1958).

2.8 MUSCULOSKELETAL

No studies were identified regarding musculoskeletal effects in humans after inhalation, oral, or dermal exposure to 1,1,1-trichloroethane.

No lesions were found in the muscles or bones of rats and mice exposed to concentrations up to 1,500 ppm for 2 years via inhalation (Quast et al. 1988).

No reported non-neoplastic lesions in muscle or bone were observed in rats exposed to 1,500 mg/kg/day or mice to 5,615 mg/kg/day by gavage in corn oil for 78 weeks (NCI 1977).

No studies were identified regarding the musculoskeletal effects in animals after dermal exposure.

2.9 HEPATIC

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

Serum liver enzymes were normal in individuals acutely exposed by inhalation to 1,1,1-trichloroethane at concentrations up to 10,000 ppm (Stewart et al. 1961; Torkelson et al. 1958). In a matched-pair occupational study of textile workers, exposure to 1,1,1-trichloroethane levels <250 ppm did not affect serum liver enzymes in individuals (Kramer et al. 1978). Results from tests for hepatic function (not described) were within the normal range in 28 workers exposed to unspecified concentrations of 1,1,1-trichloroethane for an average of approximately 17.6 years (Kelafant et al. 1994). Some case studies of individuals exposed to high 1,1,1-trichloroethane concentrations did report elevated hepatic serum enzyme levels. Three individuals who had substantial occupational exposure to 1,1,1-trichloroethane had elevated (>2-fold) serum alanine aminotransferase (ALT) levels (Hodgson et al. 1989). An individual studied by Halevy et al. (1980) had elevated levels of serum bilirubin, lactate dehydrogenase (LDH), alkaline phosphatase, and aspartate aminotransferase (AST). Elevated serum AST (5-fold), ALT (3-fold), LDH (2-fold), gamma-glutamyl transpeptidase (GGT) (2-fold), and pathologic signs of progressive liver disease (fibrosis, nodule formation, regeneration, and granulomas) were noted in a patient who was occupationally exposed to unknown concentrations of 1,1,1-trichloroethane for several years (Cohen and Frank 1994). Removal of the patient from exposure resulted in improvement of the impaired liver function, although the serum levels of LDH, GGT, AST, and ALT remained higher than normal as long as 14 months following cessation of exposure. Other exposed individuals did not have elevated serum hepatic enzyme levels (Stewart 1971; Wright et al. 1984). In some cases, histopathological examination revealed mild fatty changes in the liver of individuals exposed to high 1,1,1-trichloroethane concentrations (Caplan et al. 1976; Hall and Hine 1966; Hodgson et al. 1989). In another case, cholestasis was observed (Halevy et al. 1980). Pathological liver effects were observed in two separate case reports of repeated exposure to 1,1,1-trichloroethane in poorly ventilated work areas (Croquet et al. 2003; Texter et al. 1979).

In several studies, acute-duration exposure to high 1,1,1-trichloroethane concentrations did not affect serum enzyme levels, liver weights, or histopathology in rats, mice (Carlson 1973; Cornish and Adefuin 1966; Gehring 1968; Savolainen et al. 1977), dogs (Herd et al. 1974), or rabbits (BRRC 1987b). Rats exposed to 2,500 ppm for 24 hours had increased absolute and relative liver weights (Fuller et al. 1970).

Continuous exposure to 1,1,1-trichloroethane at concentrations up to 400 ppm for 10 days resulted in increased relative liver weights in rats (Koizumi et al. 1983); however, in the absence of data on hepatic serum enzymes or histopathological assessments, the toxicological significance of this finding is uncertain. Acute-duration inhalation exposure to 8,000 ppm 1,1,1-trichloroethane for up to 7 hours resulted in a 12% increase in relative liver weights and slight fatty changes of the liver in male Wistar rats (Adams et al. 1950). No adverse effects on the liver (liver weights, serum enzymes, histopathology) were observed in rats exposed to up to 500 ppm for acute durations (Savolainen et al. 1977; Schwetz et al. 1975).

Intermediate-duration exposure to 1,1,1-trichloroethane produced hepatic effects in animals including mild histopathological changes in the liver and effects on liver enzymes. Intermediate-duration exposure to 800 ppm 1,1,1-trichloroethane resulted in increased liver weights by 15% and liver-to-body-weight ratios by 16% (Toftgard et al. 1981); however, in the absence of data on hepatic serum enzymes or histopathological assessments, the toxicological significance of these findings is uncertain. Increased centrilobular fat accumulation and hepatic triglycerides were reported in mice exposed to 1,000 ppm for 14 weeks (MacEwen and Vernot 1974). Histopathological effects in mice exposed to 1,000 ppm 1,1,1-trichloroethane continuously for 14 weeks included hepatocyte vacuolation, degeneration, and necrosis (McNutt et al. 1975). Necrosis was first observed after 10 weeks of exposure and was observed in 40% of exposed mice after 12 weeks. McNutt et al. (1975) also reported increased liver triglycerides and an increase in relative liver weights at all time points (weeks 1–14) and increased absolute liver weights at week 12. Torkelson et al. (1958) reported increased relative liver weights and centrilobular fatty changes in guinea pigs exposed to 1,000 ppm for 3 months. Exposure to 5,000 ppm 1,1,1-trichloroethane for 45 days resulted in slight to moderate central fatty degeneration in the liver of guinea pigs (Adams et al. 1950). However, no effects were observed in guinea pigs exposed to 650 ppm for 58 or 93 days, 1,500 ppm for 60 days, or 3,000 ppm for 29 days (Adams et al. 1950). No adverse effects on the liver were noted in several species (monkeys, rats, mice, guinea pigs) exposed to up to 5,000 ppm for up to 6 months (Adams et al. 1950; Calhoun et al. 1981; MacEwen and Vernot 1974; Prendergast et al. 1967; Torkelson et al. 1958; Truffert et al. 1977; York et al. 1982).

Rats exposed to 1,500 ppm for 2 years exhibited a reduction in hepatocyte size, accentuated lobular pattern, and altered centrilobular cytoplasmic staining (Quast et al. 1988). No effects were observed in mice exposed similarly in the same study. No hepatic effects were observed in mice or rats exposed to approximately 3200 ppm for 104 weeks (Ohnishi et al. 2013)

In a case in which a man who ingested an estimated dose of 600 mg/kg/day of 1,1,1-trichloroethane, serum bilirubin levels became slightly elevated after 48 hours but serum aminotransferase levels (i.e., ALT, AST) remained within normal limits (Stewart and Andrews 1966).

No changes in serum hepatic enzymes were observed in rats given a single oral dose of 13 mg/kg 1,1,1-trichloroethane (Tyson et al. 1983). Similarly, in rats orally exposed for 11 days to doses up to 10,000 mg/kg/day 1,1,1-trichloroethane, no toxicologically significant increases were observed on serum ALT or AST (Bruckner et al. 2001). There were no changes in serum enzymes or liver weights in rats exposed to 1,1,1-trichloroethane at a dose of 1,650 mg/kg/day for 7 days (Platt and Cockrill 1969).

No hepatic effects were observed in rats administered gavage doses of up to 5,000 mg/kg/day for 7–13 weeks (Bruckner et al. 2001). Decreased absolute (17%) and relative (12%) liver weights in female rats administered 4,800 mg/kg/day and decreased absolute (13%) liver weights in male rats administered 5,000 mg/kg/day of 1,1,1-trichloroethane in the diet for 13 weeks were observed but were attributed to reduced body weights, rather than adverse liver effects (NTP 2000). No effects on hepatic serum enzyme levels, liver weights, or histology were seen in male or female mice receiving doses up to as high as 15,000 and 23,000 mg/kg/day, respectively, for 13 weeks (NTP 2000).

Chronic-duration gavage administration of 1,1,1-trichloroethane up to 1,500 mg/kg/day did not affect the incidence of nonneoplastic lesions in the livers of rats or mice (NCI 1977).

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

In rats dermally exposed to 280 mg/kg/day of 1,1,1-trichloroethane under occlusion for 3 weeks, no effect on serum levels of hepatic enzymes AST, ALT, and ALP were observed (Viola et al. 1981). Histopathological effects observed included fatty degeneration, mitochondrial swelling in hepatocytes, and inflammatory infiltrates (Viola et al. 1981). A study in which rabbits were dermally exposed without occlusion to 500 ppm 1,1,1-trichloroethane for 90 days did not reveal histopathological effects in the liver or changes in liver weight (Torkelson et al. 1958).

Mechanism of Action. 1,1,1-Trichloroethane causes mild to moderate hepatotoxic effects in humans and animals through cytochrome P-450-mediated dechlorination, which leads to liver injury (Plaa 1986). This mechanism of toxicity hypothesizes that the production of free radicals via the homolytic cleavage of the

carbon-chlorine bond in these hepatotoxic chlorinated alkanes occurs in the endoplasmic reticulum of hepatocytes and that the free radicals react with unsaturated lipids and proteins in the endoplasmic reticulum, producing lipid peroxidation and covalent binding, which leads to morphological and functional changes in the organelle eventually leading to cellular dysfunction and necrosis (Plaa 1986). Two studies evaluating the ability of 1,1,1-trichloroethane to induce hepatic drug metabolism reported induced activity of liver microsomal enzymes (e.g., cytochrome P-450, nicotinamide adenine dinucleotide phosphate, reduced form [NADPH], cytochrome c reductase) in rats and mice (Fuller et al. 1970; Lal and Shah 1970). Exposure to up to 400 ppm for 10 days also increased microsomal enzyme activity in rats but exposure to 800 ppm 1,1,1-trichloroethane suppressed hepatic mixed-function oxidative system after 48 hours (Koizumi et al. 1983). A 5-day repeated exposure to 500 ppm 1,1,1-trichloroethane decreased microsomal cytochrome P-450 levels in rats (Savolainen et al. 1977). Intermediate-duration exposure to 800 ppm 1,1,1-trichloroethane had no effect on microsomal enzyme levels in rats (Toftgard et al. 1981). Reduced levels of cytochrome P-450 and epoxide hydratase in rats suggests inhibition of these enzymes (Vainio et al. 1976).

2.10 RENAL

No adverse effects on kidneys, as measured by serum levels of blood urea nitrogen (BUN), uric acid, and creatinine, were reported in a matched pair occupational study of textile workers chronically exposed to <250 ppm 1,1,1-trichloroethane (Kramer et al. 1978). In a retrospective cohort study of aircraft workers, those exposed to 1,1,1-trichloroethane had a >2.37-fold risk of end-stage renal disease (odds ratio [OR] 2.37, 95% confidence interval [CI] 1.02, 5.49) compared to unexposed workers (Radican et al. 2006).

Acute-duration inhalation exposure to 1,1,1-trichloroethane concentrations up to 12,000 ppm did not affect kidney weights or histology in rats (Adams et al. 1950; Cornish and Adefuin 1966).

Exposure of several animal species to moderate to high concentrations of 1,1,1-trichloroethane for intermediate durations had no apparent effect on relevant serum chemistry parameters, kidney weight, or histopathology (Adams et al. 1950; Calhoun et al. 1981; Eben and Kimmerle 1974; Kjellstrand et al. 1985b; MacEwen and Vernot 1974; Prendergast et al. 1967; Torkelson et al. 1958; Truffert et al. 1977).

Chronic-duration inhalation of 1,1,1-trichloroethane did not affect the kidneys of rats or mice (Quast et al. 1988). However, female F344 rats exhibited increased relative, but not absolute, kidney weights after exposure to 3,181 ppm 1,1,1-trichloroethane for 6 hours/day, 5 days/week for 104 weeks (Ohnishi et al.

2013). The effect on relative kidney weights were observed only in the female rats, which were also the only group to have a decrease in body weight, and were not observed in male F344 rats, nor in male or female BDF1 mice exposed to 3,204 ppm 1,1,1-trichloroethane for the same duration (Ohnishi et al. 2013).

Normal BUN levels were reported in the case of a man who accidently ingested approximately 600 mg/kg 1,1,1-trichloroethane (Stewart and Andrews 1966).

No effects on kidney weights or histology were found in rats given a single gavage dose of 4,000 mg/kg/day or repeated doses of 10,000 mg/kg/day for 11 days (Bruckner et al. 2001). There was no histopathological evidence of renal damage in male rats administered 165 mg/kg/day of 1,1,1-trichloroethane by gavage for 21 days (NTP 1996). Urinalysis results showed increases in mean urinary protein; however, the statistical significance of this finding is questionable since it was based on only four surviving rats.

No effects on kidney weight or histology were found in rats with 13-week exposure to 5,000 mg/kg/day (Bruckner et al. 2001). In another study, similarly exposed rats had no treatment-related kidney effects (NTP 2000). Male rats in this study exhibited kidney lesions indicative of hyaline droplet formation; however, this effect is specific to male rats and is not a human health concern.

Chronic-duration oral exposure to 1,1,1-trichloroethane in rats and mice at doses of 1,500 and 5,615 mg/kg/day, respectively, had no effect on the incidence of nonneoplastic lesions in the kidneys (NCI 1977).

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

No kidney lesions were reported for intermediate-duration dermal exposure to 1,1,1-trichloroethane at doses of 280 mg/kg/day in rats or 500 mg/kg/day rabbits (Torkelson et al. 1958; Viola et al. 1981).

2.11 DERMAL

No information on dermal effects in humans exposed to inhaled 1,1,1-trichloroethane were evaluated. Case-control studies on scleroderma are discussed in Section 2.14.

Whole-body exposure to 4,000 ppm 1,1,1-trichloroethane in the air for 4 hours caused the fur coat of mice to become dull (Evans and Balster 1993). Rats and mice exposed to 2,000 ppm 1,1,1-trichloroethane for 90 days did not have any dermal effects (Calhoun et al. 1981). Dermal lesions were not reported in mice exposed to 1,1,1-trichloroethane via inhalation for 2 years at a concentration of 1,500 ppm (Quast et al. 1988).

No studies were identified regarding dermal effects of oral exposure to 1,1,1-trichloroethane in humans. No non-neoplastic lesions were reported in rats or mice exposed to 1,1,1-trichloroethane at concentrations of 1,500 or 5,615 mg/kg/day, respectively, for 78 weeks (NCI 1977).

Dermal exposure to 1,1,1-trichloroethane in humans causes dermal effects that are reversible upon cessation of exposure. Stewart and Dodd (1964) had volunteers immerse their thumbs in a beaker of 1,1,1-trichloroethane for 30 minutes. After 10 minutes of exposure, subjects reported a mild burning sensation and post-exposure, erythema and fine scaling were observed on the thumbs. Symptoms resolved after an hour. Similar results were reported when the subjects immersed their entire hand into the beaker, with a more intense and rapid onset. Walhberg (1984b) reported similar symptoms after a 5-minute dermal exposure to 30 mg/kg 1,1,1-trichloroethane along with an increase in blood to the skin, which subsided after an hour. A subsequent experiment where subjects were dermally exposed to 2 mg/kg 1,1,1-trichloroethane for 10 days reported no adverse effect on skin-fold thickness or any apparent skin reactions (Wahlberg 1984a). In a case study, a 30-year-old man developed contact dermatitis, identified using skin patch testing, after occupational exposure to 1,1,1-trichloroethane for 3 years (Ingber 1991).

Dermal effects from 1,1,1-trichloroethane exposure in animals are mild and transient. Torkelson et al. (1958) reported slight reddening and scaliness of the skin of rabbits after a 1-day exposure to 3,980 mg/kg and slightly worse irritation after 10-day repeated exposures. Symptoms quickly resolved once exposure ceased. Histological examination noted degenerative changes in the epidermis (karyopyknosis, karyolysis, perinuclear edema, and spongiosis) in the skin of guinea pigs following exposure to undiluted 1,1,1-trichloroethane under a cover glass for durations ranging from 15 minutes to 16 hours (Kronevi et al. 1981). In addition, the upper part of the dermis had focal junctional separation and cellular infiltration. Effects were seen within 15 minutes of exposure and were still present 16 hours later. Skin sensitization assays are reviewed in Section 2.14.

Slight skin irritation was also reported in rabbits following a 13-week exposure to 1,1,1-trichloroethane at doses ranging from 15 to 500 mg/kg/day (Torkelson et al. 1958). Skin-fold thickness increased by 81% in rabbits and 41% in guinea pigs exposed to dermal applications of 1,1,1-trichloroethane at concentrations of 35 and 220 mg/kg/day, respectively, for 10 days (Wahlberg 1984a). Visible erythema and edema were present within 24–72 hours of the original exposure (Wahlberg 1984a).

2.12 OCULAR

Mild eye irritation was reported in volunteers exposed to 1,1,1-trichloroethane at air concentrations >1,000 ppm for durations ranging from 15 to 73 minutes (Stewart et al. 1961). Eye irritation, hyperemia, and photophobia were observed in "some" volunteers exposed to 450 ppm for 8 hours; incidence and severity were not reported (Salvini et al. 1971). In contrast, no eye irritation was reported when the 1,1,1-trichloroethane concentration was 500 ppm for 186 minutes (Stewart et al. 1961).

No treatment-related ocular effects were observed in mice or rats after a 6-hour inhalation exposure to 4,946 ppm 1,1,1-trichloroethane (Calhoun et al. 1981); however, periocular porphyrin pigmentation was observed transiently. Eye irritation was reported in rabbits continuously exposed to 4,000 ppm 1,1,1-trichloroethane for 4 days (Evans and Balster 1993). The eye irritation may be the result of direct chemical contact with the eye. There were no effects observed in rats or mice after exposure to concentrations of 2,000 ppm 1,1,1-trichloroethane for 90 days (Calhoun et al. 1981). No ocular lesions were observed in rats exposed to 1,1,1-trichloroethane at a concentration of 1,500 ppm for 2 years (Quast et al. 1988).

No studies were identified regarding ocular effects of oral exposure to 1,1,1-trichloroethane in humans or animals.

Individuals briefly exposed to 1,1,1-trichloroethane vapor concentrations of 2,650 ppm (progressive exposure from 0 to 2,650 ppm) reported mild eye irritation likely due to ocular direct contact (Stewart et al. 1961).

Ocular administration of 1,1,1-trichloroethane caused only mild eye irritation in rabbits (Krantz et al. 1959; Marzulli and Ruggles 1973; Torkelson et al. 1958). Marzulli and Ruggles (1973) conducted Draize eye testing in rabbits in 10 laboratories; little to no eye irritation was observed following exposure to 0.1 mL undiluted 1,1,1-trichloroethane. Although eye irritation produced by direct application of

1,1,1-trichloroethane seems to be minor, mice exposed continuously to 4,000 ppm 1,1,1-trichloroethane in the air for 4 hours exhibited eye irritation during exposure (Evans and Balster 1993).

2.13 ENDOCRINE

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

Information on endocrine effects in animals is limited. In an acute-duration study, no histopathological changes were seen in the adrenal glands of male rats after a single 2-hour exposure to up to 15,000 ppm 1,1,1-trichloroethane (Cornish and Adefuin 1966). Plasma corticosterone levels were significantly decreased in male rats after inhalation exposure to 1,1,1-trichloroethane at a concentration of 3,500 ppm for 30 minutes (30%) or 5,000 ppm for 10 (25%) or 30 minutes (50%) (Pise et al. 1998). Plasma adrenocorticotropic hormone was decreased by 50 and 60% at 5,000 ppm after 10 and 30 minutes, respectively.

No studies were identified regarding endocrine effects in humans or animals following oral or dermal exposure to 1,1,1-trichloroethane.

2.14 IMMUNOLOGICAL

Available information on immunological effects of 1,1,1-trichloroethane in humans is limited to two case-control studies. Dow Corning Corp (1994) reported a positive association between purported exposure to 1,1,1-trichloroethane and increased risk of systemic sclerosis (scleroderma) in 377 Michigan women. Controlling for confounding was limited. A larger, follow-up case-control study conducted on 660 women diagnosed with scleroderma between 1980 and 1992 in Michigan and Ohio found no association between exposure to 1,1,1-tricloroethane and scleroderma (Garabrant et al. 2003). In both case-control studies, 1,1,1-trichloroethane exposure could not be quantified.

Acute-duration exposure to 1,1,1-trichloroethane for 2 hours at concentrations up to 15,000 ppm did not result in any histopathological changes to the spleen in Sprague-Dawley rats (Cornish and Adefuin 1966). A 3-hour exposure to 350 ppm 1,1,1-trichloroethane did not have immunological effects on lung host defense (as measured by susceptibility to infection with *Streptococcus zooepidemicus* challenge and

bactericidal activity of alveolar macrophages) in CD-1 mice (Aranyi et al. 1986). Mice exposed under similar conditions for 5 days produced similar results.

Intermediate-duration exposures did not result in any changes in spleen weight or any histopathological changes in several animal species at concentrations up to 2,210 ppm (Prendergast et al. 1967; Torkelson et al. 1958). Similarly, no histopathological changes in the spleen and thymus were reported in rats or mice exposed to 1,1,1-trichloroethane at concentrations up to 1,500 ppm for 2 years (Quast et al. 1988).

There was no effect on the incidence or type of non-neoplastic lesions in the thymus or spleen in rats or mice after 1,1,1-trichloroethane administration via gavage to 1,500 or 5,615 mg/kg/day, respectively, for 78 weeks (NCI 1977).

A single application of 1,1,1-trichloroethane to the mouse ear resulted in significantly increased ear thickness approximately 2 hours following treatment (Iyadomi et al. 2000). Dermal exposure to 500 mg/kg/day without occlusion in a 90-day study did not result in changes to spleen weight or histopathology in rabbits (Torkelson et al. 1958).

2.15 NEUROLOGICAL

Results of acute-duration inhalation studies in humans showed impaired performance in tests designed to measure cognitive and psychomotor skills with variables such as manual dexterity, eye-hand coordination, perceptual speed, and reaction time at concentrations as low as 175 ppm (Gamberale and Hultengren 1973; Mackay et al. 1987). Syntactic reasoning was unaffected by 1,1,1-trichloroethane exposure, but distractibility, as measured by the Stroop test, was improved in the study by Mackay et al. (1987), suggesting that impairment produced by 1,1,1-trichloroethane may be task-specific. Mackay et al. (1987) exposed 12 men to concentrations of 0, 175, or 350 ppm of 1,1,1-trichloroethane for 3.5 hours, administering three psychomotor (simple reaction time, choice reaction time, and tracking ability) and two cognitive (syntactic reasoning and concentration) tasks immediately before entering the exposure chamber, and 20, 60, 120, and 180 minutes after entry. The tests for simple reaction time, choice reaction time, and tracking ability all showed impaired psychomotor performance in volunteers exposed to 1,1,1-trichloroethane concentrations of 175 and 350 ppm. Effects were detected as soon as 20 minutes after the start of exposure at both concentrations. The test for simple reaction time appeared to be the most sensitive, exhibiting a 10–15% increase over baseline values. Observed performance changes correlated with 1,1,1-trichloroethane absolute blood levels. Performance in the cognitive tasks was not

adversely affected by exposure, and neither was the self-reported mood of the volunteers. In males exposed to 500 ppm for 5 days, alterations were observed in electroencephalograph (EEG) tracings; no changes were observed in females exposed to 350 ppm under the same exposure conditions (NIOSH 1975). In other studies, exposures up to 450 ppm for up to 6 hours did not produce significant psychomotor effects (Salvini et al. 1971) or produced only weak effects (Savolainen et al. 1981). Note that Savolainen et al. (1981) exposed some subjects to a single exposure of xylene 1 week before exposure to 1,1,1-trichloroethane. Although these studies examined some of the same parameters, such as reaction time, different analytical methods were used, and different subpopulations were tested. In another study using nine healthy, male volunteers who were exposed to a time-weighted average concentration of 200 ppm 1,1,1-trichloroethane for 5 hours, including six 10-minute periods of exercise, Laine et al. (1996) found no significant effects on electroencephalogram or visual evoked potentials and no subjective symptoms. However, Muttray et al. (2000) reported significantly increased subjective tiredness scores and electroencephalogram changes consistent with increased drowsiness following a 4-hour inhalation exposure of 12 healthy male volunteers to 200 ppm of 1,1,1-trichloroethane. Each of the studies described above have various limitations, including the use of small sample sizes, use of healthy volunteers, and use of only male subjects.

Gross neurobehavioral effects, such as disturbances of equilibrium and coordination, have been observed in humans following acute-duration exposure to 1,1,1-trichloroethane. Torkelson et al. (1958) reported adverse changes in equilibrium and coordination (Rhomberg test and self-reported lightheadedness) in volunteers exposed to 900 ppm for 75 minutes. Stewart et al. (1961) also reported lightheadedness in two of six volunteers exposed to 900 ppm for 3 hours. Later, two volunteers exposed to 500 ppm for 3 hours experienced disequilibrium; however, reports in two subjects were confounded by reports of disequilibrium in the same subjects prior to exposure, and some volunteers reported “feeling sleepy” while performing repetitive tests (Stewart et al. 1969). Laine et al. (1996) found no significant effects on equilibrium after 200 ppm of 1,1,1-trichloroethane exposure for 5 hours.

No exposure-related effects were found, based on the results of subjective questionnaires, neurological examinations, and psychological tests, in an occupational study with exposures from 200 to 990 ppm and an average duration of 6.7 years (Maroni et al. 1977). Maroni et al. (1977) suggested that no definitive conclusions can be drawn due to the small sample size of six to seven subjects per group and short duration of exposure. However, a study of 28 workers occupationally exposed to high “near anesthetic levels” of unspecified concentrations of 1,1,1-trichloroethane over an average period of 17.6 years revealed deficits in memory and in several components of balance (Kelafant et al. 1994). Deficits in

memory, attention, and concentration were also diagnosed in a 45-year-old man who had been heavily exposed to 1,1,1-trichloroethane, as well as dichloromethane, for 15 years (Garnier et al. 1991). Although the patient's brain function slowly improved following removal from exposure, lingering memory deficits were noted in a follow up 5 years later.

The principal neurological effects observed in animals exposed to 1,1,1-trichloroethane are signs of central nervous system depression, ataxia, unconsciousness, and impaired performance in behavioral tests; these are summarized below.

Neuromotor. Clinical signs of ataxia, narcosis, and unconsciousness were commonly observed in several acute-duration studies. Acute-duration exposure to concentrations up to 7,800 ppm produced intoxication and incoordination in rats (Clark and Tinston 1982; Hougaard et al. 1984). Clinical signs of narcosis were observed in rats exposed to 5,000 ppm for up to 7 hours, with unconsciousness observed at doses of 18,000 ppm (Adams et al. 1950). Ataxia, narcosis, and unconsciousness have been reported in rats following acute-duration exposures to 1,1,1-trichloroethane at concentrations of 23,000 ppm for 30 minutes (Woolverton and Balster 1981), 3,080 ppm for up to 4 hours (Mullin and Krivanek 1982), 7,800 ppm for up to 2 hours (Hougaard et al. 1984), and 8,000 ppm 3 times/day for 1 hour on gestation days (GDs) 12–17 (Jones et al. 1996). Jones et al. (1996) also reported mild tremors and gait abnormalities in dams. Dams exposed to 7,000 ppm 1,1,1-trichloroethane 3 times/day for 1 hour on GDs 13–19 exhibited clinical signs that included salivation, lacrimation, and abnormal gait (Coleman et al. 1999). Sprague-Dawley rats had clinical signs of somnolence after exposure to 10,000 ppm for 6 hours, compared with pre-exposure (Bonnet et al. 1980). Impaired placing, grasping, lift, and righting reflexes were reported in rats exposed to 3,080 ppm for up to 4 hours (Mullin and Krivanek 1982). Impaired righting reflex, motor coordination, and/or strength, measured by an inverted screen test, were observed in mice exposed to 5,173 ppm 1,1,1-trichloroethane for 30 minutes (Woolverton and Balster) and 10,000 ppm 1,1,1-trichloroethane for 20 minutes (Bowen et al. 1996b). Motor incoordination was reported following a 6-hour inhalation exposure to 4,946 ppm 1,1,1-trichloroethane in male CDF rats (Calhoun et al. 1981). Bowen and Balster (2006) observed increased locomotor activity (by 70–250%) following a 30-minute exposure to 6,000 ppm 1,1,1-trichloroethane in male mice. Increased motor activity was observed in several studies in mice exposed to 1,250 to 4,000 ppm 1,1,1-trichloroethane for 30 minutes/day for 2–5 days (Balster et al. 1997; Bowen and Balster 1996, 1998). Increased motor activity was also reported in mice and rats after acute exposures to concentration ranges of 1,800–8,000 ppm (Horiguchi and Horiuchi 1971; Kjellstrand et al. 1985a; Moser and Balster 1985; Moser et al. 1985).

Ataxia and narcosis were reported in rats following exposures to concentrations of 10,000 ppm 1,1,1-trichloroethane for 3 months (Torkelson et al. 1958). Increased locomotor activity was reported in a 15-day study of daily 30-minute exposures to 6,000 ppm (Bowen and Balster 2006). Mattsson et al. (1993) conducted a 13-week study in rats that underwent functional observational battery and foregrip strength testing pre-exposure and monthly thereafter during exposure, and functional observational battery (FOB), neurophysiological testing, and neuropathology after exposure. No adverse effects were noted other than a deficit in forelimb grip performance at 2,210 ppm in both male and female rats, which persisted for 7 weeks beyond the end of the exposure period (Mattsson et al. 1993). Histopathological and electrophysiological evaluation found no evidence of neuropathy in the forelimb that might account for this result and the study authors hypothesized that sedative properties of 1,1,1-trichloroethane may have been responsible by allowing the animals to become more relaxed and, consequently, more habituated to the test procedure (Mattsson et al. 1993).

Neurosensory. No ototoxic effects were observed in rats exposed to up to 2,210 ppm 1,1,1-trichloroethane for 13 weeks (Mattsson et al. 1993; Vyskocil et al. 2010). No ototoxic effects were reported in a weight-of-evidence study in which data from the Quebec occupational health regulation were compiled and evaluated (Vyskocil et al. 2012). In total, 44 articles, including human and animal studies evaluating the combined exposure to noise and chemicals, were compiled. No nystagmus prolongation or reduction of saccades were reported in rats exposed to up to 1,500 ppm (Niklasson et al. 1993).

Neurobehavioral. Impaired performance in behavioral tests has been reported for acute-duration inhalation exposures. Baboons exposed to 1,800 ppm for 4 hours exhibited impaired learning and memory performance as measured by a match to sample test (Geller et al. 1982). Mice exposed to 8,000 ppm for 30 minutes exhibited reduced anxiety in conditioned defensive burying task (Paez-Martinez et al. 2003). CD-1 mice exposed to 2,000 ppm for 20 minutes exhibited impaired operant learning with a 30% decrease in correct response rate (Balster et al. 1982). Inhalation of 4,000 ppm 1,1,1-trichloroethane for 30 minutes/day for 2 days decreased lever pressing in operant tasks in male albino mice by 22% (Bowen and Balster 1998). In male albino mice, exposure to 10,000 ppm for 30 minutes resulted in increased time spent in open arms (500%) and an increase in total arm entries (150%) in a radial arm maze; however, this is likely a result of hyperactivity (Bowen et al. 1996a). De Ceaurriz et al. (1983) evaluated rats in a forced swim test and found a reduced duration of immobility, which could suggest reduced behavioral despair; however, the known hyperactivity effect of 1,1,1-trichloroethane exposure makes this test difficult to interpret.

Neurophysiology. Neurophysiological changes have also been reported during acute-duration inhalation exposure to 1,1,1-trichloroethane. Continuous exposure of CFW Swiss mice to 500 ppm 1,1,1-trichloroethane for 4 days resulted in a withdrawal syndrome characterized by handling-induced seizures in 5/10 mice and reduced threshold to pentylenetetrazol-induced seizures after exposure ceased (Evans and Balster 1993). Conversely, De Ceaurriz et al. (1981) reported an EC_{50} of 6,644 ppm after a 4-hour exposure to 1,1,1-trichloroethane for elevation of the threshold for pentetrazole-induced seizures in Swiss OF1 mice.

Neuropathology. Histopathological changes in the brain and spinal cord tissues have been evaluated in rats and mice, but abnormalities have not been observed. Sprague-Dawley rats exposed to 2,210 ppm 1,1,1-trichloroethane intermittently for 8 hours/day, 5 days/week for 6 weeks did not show any histopathological abnormalities in the brain (Prendergast et al. 1967). F344 and CDF rats exposed to concentrations up to 2,000 ppm 1,1,1-trichloroethane vapors for 6 hours/day, 5 days/week, for 13 weeks did not show any brain histopathologic changes (Mattsson et al. 1993; Calhoun et al. 1981). F344 rats and B6C3F1 mice exposed to up to 3,200 ppm 1,1,1-trichloroethane for 6 hours/day, 5 days/week for 2 years also did not show any histopathological changes in the brain (Ohnishi et al. 2013; Quast et al. 1988).

Neurochemistry. Changes in brain metabolism have been reported in rats and mice after acute-duration inhalation exposure to 1,1,1-trichloroethane; however, the toxicological significance of these findings is unclear. Cerebral glucose consumption was decreased by 14–55% in rats exposed to 6,000 ppm for 2 hours (Hougaard et al. 1984). There were reported decreases in expression levels of cyclic nucleotides (cGMP and cAMP) in rats and mice exposed to up to 5,000 ppm for up to 4 hours (Nilsson 1986a, 1986b; You and Dallas 2000). While the protein levels of cyclic nucleotides were evaluated, enzyme activity was not; therefore, these are of unclear relevance. The only effect observed in rats exposed to 8,000 ppm for up to 60 minutes was increased lactate expression in the brain, suggesting possible energy dysfunction; however, in isolation, the toxicological significant of this finding is uncertain (Folbergrova et al. 1984). Páez-Martinez et al. (2008) observed a decrease in mu-opioid receptor binding in the thalamus and periaqueductal gray, as well as an increase in benzodiazepine receptor binding in the caudate putamen, in Swiss-Webster mice after a 30-minute exposure to 12,000 ppm 1,1,1-trichloroethane. Savolainen et al. (1977) did not report any adverse effects on the levels of protein, glutathione, acid proteinase, or ribonucleic acid (RNA) in the brain in rats acutely exposed to 500 ppm 1,1,1-trichloroethane. Continuous exposure to 1,200 ppm 1,1,1-trichloroethane for 30 days altered the fatty acid

composition of ethanolamine phosphoglyceride isolated from the cerebral cortex in rats (Kyrklund and Haglid 1991). No effects on brain fatty acid composition were reported in a similar study with exposure to 320 ppm (Kyrklund et al. 1988).

Markers of damage to neurological tissues have been observed in intermediate-duration studies. In an intermediate-duration study, brain injury resulting in reactive gliosis was evaluated by examining the number and/or size of astrocytes in the area as measured by the quantification of the proteins, glial fibrillary acid protein (GFAP) and astroglial protein S-100. A significant increase in GFAP was observed in the sensorimotor cerebral cortex in gerbils 4 months after exposure to 210 ppm 1,1,1-trichloroethane (Rosengren et al. 1985). Rosengren et al. (1985) did not report any increase in the levels of S-100 after exposure to this dosing regimen.

There were no neurological abnormalities reported in a man who ingested an estimated 600 mg/kg of 1,1,1-trichloroethane 4 hours earlier (Stewart and Andrews 1966).

In an 11-day oral study, Sprague-Dawley rats exposed to 5,000 mg/kg/day 1,1,1-trichloroethane exhibited hyperexcitability followed by narcosis (Bruckner et al. 2001). Intermediate-duration oral exposure to 2,500 mg/kg/day for 13 weeks (5 days/week) via gavage oil in Sprague-Dawley rats caused hyper-excitability followed by hours of narcosis after dosing (Bruckner et al. 2001). There were no reported clinical signs of neurotoxicity in a 13-week study of rats and mice exposed to 1,1,1-trichloroethane at doses up to 5,000 mg/kg/day in the diet (NTP 2000).

Neurophysiological alterations were evaluated in rats exposed orally to 705 mg/kg/day of 1,1,1-trichloro-ethane for 4 days (Spencer et al. 1990). After 2 days of exposure, no behavioral or appearance changes were detected by FOB. However, after 4 days, neurophysiological alterations present including marked changes in the flash-evoked potential, electroencephalogram recordings, and smaller changes in somatosensory-evoked potential.

No changes in type or incidence of lesions of neurological tissues were reported in a 78-week gavage study of rats and mice exposed to 1,1,1-trichloroethane at doses of up to 1,500 and 5,615 mg/kg/day, respectively (NCI 1977).

Occupational exposure to 1,1,1-trichloroethane caused peripheral neuropathy in three women with the initial symptoms including numbness in their limbs, and subsequent nerve conduction studies showed

alterations in peripheral nerve activity (Howse et al. 1989; Liss 1988). Occupational exposure was likely to be a combination of inhalation and dermal exposures; however, exposure levels were not reported. Subsequent examination 3–4 years after diagnosis in the form of sural nerve biopsies in two of the women revealed chronic-duration neuropathy (axonopathy and myelinopathy) (Liss 1988). Peripheral neuropathy was also reported following exposure to 1,1,1-trichloroethane used as a degreasing agent in two additional case studies (House et al. 1994, 1996).

In animals, neurological effects of dermal exposure were limited to histopathology examination that did not find any lesions or other changes in the brains of rabbits exposed to 500 mg/kg/day of 1,1,1-trichloroethane for 90 days (Torkelson et al. 1958).

Mechanism of Action. Respiratory arrest due to central nervous system depression has been proposed as a possible explanation for sudden deaths following acute exposure to high concentrations of 1,1,1-trichloroethane (Adams et al. 1950; Jones and Winter 1983; Torkelson et al. 1958). In general, the actions of 1,1,1-trichloroethane are very similar to other central nervous system depressants. The mechanism by which acute-duration exposures to high concentrations of 1,1,1-trichloroethane depress the central nervous system is thought to involve interactions of the parent compound with lipids and/or proteins in neural membranes that lead to dysfunction (Evans and Balster 1991). The highly lipophilic nature of chlorinated hydrocarbons, such as 1,1,1-trichloroethane, allows them to cross the blood-brain barrier readily and partition into lipids in neuronal membranes. This property allows them to interfere with neural membrane function, bringing about central nervous system depression, behavioral changes, and anesthesia (Klaassen et al. 1996). It is hypothesized that trichloroethanol, a minor metabolite of 1,1,1-trichloroethane, also interacts with hydrophobic portions of cell proteins thereby altering ligand-gated channels of cell membranes, which may lead to potentiation of gamma-aminobutyric acid (GABA)-mediated responses causing inhibition of excitatory signals (Peoples and Weight 1994; Peoples et al. 1990; Savolainen et al. 1977).

2.16 REPRODUCTIVE

Limited information is available regarding the reproductive toxicity of 1,1,1-trichloroethane in humans, and exposure levels have not been quantified. Taskinen et al. (1989) conducted a case-control epidemiology study to investigate the relationship between adverse pregnancy outcomes (spontaneous abortions and congenital malformations) and occupational exposure of fathers to organic solvents, including 1,1,1-trichloroethane, during spermatogenesis for the 80 days prior to conception. No

relationship was found between exposure to 1,1,1-trichloroethane and adverse pregnancy outcomes. Other case-control studies that investigated the relationship between spontaneous abortions and maternal exposure to solvents, including 1,1,1-trichloroethane, also found no clear evidence of a relationship (Lindbohm et al. 1990). A cohort study examined decreases in fertility (as measured by number of menstrual cycles required until pregnancy achieved) involving Finnish male workers with exposure to 1,1,1-trichloroethane and found no association between the women whose partners were exposed to 1,1,1-trichloroethane and number of menstrual cycles before becoming pregnant (Sallmen et al. 1998).

In acute-duration studies, no effects on maternal body weight gain during gestation, gestation length, or litters produced were reported in CD-1 mice exposed to 2,000 ppm 1,1,1-trichloroethane for 17 hours (Jones et al. 1996). No reproductive effects (mean implantations per litter, litter size, or resorptions) were reported in mice exposed to 875 ppm during GDs 6–15 (Schwetz et al. 1975), mice exposed to 8,000 ppm for 1 hour, 3 times/day, during GDs 12–17 (Jones et al. 1996) or rabbits exposed to 1,000 ppm during GDs 6–18 (BRRC 1987b). Continuous exposure to 625 ppm of 1,1,1-trichloroethane vapor for 30 days had no effect on butyrylcholinesterase activity in mice, suggesting no effect on testosterone activity (Kjellstrand et al. 1985a). Significant increases in gestation length were noted in pregnant rats exposed to 7,000 ppm 1,1,1-trichloroethane 3 times/day for 1 hour on GDs 13–19 (Coleman et al. 1999). Litters were completely resorbed in two of nine exposed dams.

In an intermediate-duration study, Adams et al. (1950) reported that exposure to 5,000 ppm 1,1,1-trichloroethane for 45 days (5 days/week, 7 hours/day) caused testicular degeneration in guinea pigs; however, the incidences and severity were not provided; therefore, the toxicological significance is uncertain. No effects on weights or histology of reproductive organs were observed in rats exposed to up to 5,000 ppm for 44 days (testes weights) (Adams et al. 1950), 1,976 ppm for 90 days (Calhoun et al. 1981), 500 ppm for 6 months (Torkelson et al. 1958), or 1,100 for 15 weeks (Truffert et al. 1977); mice exposed to 1,976 ppm for 13 weeks (Calhoun et al. 1981); or guinea pigs exposed to up to 3,000 ppm for up to 6 months (Adams et al. 1950; Torkelson et al. 1958). No effects were observed in a comprehensive reproductive and developmental study in rats exposed to 2,100 ppm for approximately 52 days (York et al. 1982).

Histological examination of male and female reproductive tissues revealed no exposure-related changes in rats, mice, or rabbits following chronic-duration exposure to 1,1,1-trichloroethane (Quast et al. 1988).

No studies were identified regarding reproductive effects in humans exposed orally to 1,1,1-trichloroethane.

Limited information is available regarding reproductive effects in animals following oral exposure to 1,1,1-trichloroethane. Maternal survival, body weight, fertility, and duration of gestation were also not affected in a study in rats exposed to 1,1,1-trichloroethane in drinking water at doses up to 3 mg/kg/day for 27 or 70 days (George et al. 1989; NTP 1988a, 1988b). Epididymal spermatozoa concentrations were reduced by 10% in male rats after dietary exposure to 4,800 mg/kg/day for 13 weeks (NTP 2000). No other adverse male reproductive effects were reported in a 13-week study for male rats and mice fed 1,1,1-trichloroethane in the diet at doses of 4,800 and 15,000 mg/kg/day, respectively, and no signs of altered estrus were reported in female rats and mice exposed to 5,000 and 22,900 mg/kg/day, respectively (NTP 2000). Maternal survival, body weight, and reproductive performance were not adversely affected in a multigenerational study, in which male and female mice were exposed to 1,000 mg/kg/day of 1,1,1-trichloroethane in their drinking water with exposure beginning prior to mating and continuing through gestation and lactation for 3 generations (Lane et al. 1982).

In a chronic-duration study in rats and mice, there was no effect on the incidence or type of nonneoplastic lesions in the prostate, seminal vesicles, testes, or epididymides in males, or the uterus or ovary in females (NCI 1977).

No lesions or weight changes were found in the testes of rabbits exposed dermally to 500 mg/kg/day of 1,1,1-trichloroethane without occlusion for 90 days (Torkelson et al. 1958).

2.17 DEVELOPMENTAL

Taskinen et al. (1989) found no association between congenital malformations (not specified, as listed in the Finnish registry) and occupational exposure of fathers to organic solvents, including 1,1,1-trichloroethane, during spermatogenesis for the 80 days prior to conception in a case-control study.

Several animal studies have evaluated developmental effects of inhalation exposure to 1,1,1-trichloroethane. No effects of embryo- or fetotoxicity (fetal sex ratio, fetal weights, fetal body measurements, and anomalies) were observed in pregnant female rats and mice following exposure to 875 ppm 1,1,1-trichloroethane on GDs 6–15 (Schwetz et al. (1975). York et al. (1982) conducted a factorial study in which pregnant rats were either exposed to 2,100 ppm 1,1,1-trichloroethane before mating, during

gestation, or both. There were no signs of maternal toxicity or embryo toxicity in any test group. In offspring of dams exposed during premating and gestation, increased total skeletal anomalies were observed in 19/78 fetuses (8/20 litters) compared with 5/62 fetuses (4/15 litters) in controls and reduced clavicle size in 5/78 fetuses (5/15 litters) compared with none observed in controls. Increased total soft tissue anomalies were observed in 6/71 fetuses (6/18 litters). Pup survival, weight gain, and pup performance on neurobehavioral tests were not affected by any treatment and there were no gross lesions in offspring upon necropsy at 12 months. In rats exposed to 6,000 ppm for 4 hours a day during GDs 6–15, a 16% decrease in female fetal body weights and poorly or un-ossified cervical centra were observed (BRRC 1987a). Fetal malformations were observed in New Zealand rabbit pups after exposure during GDs 6–18 for 6 hours/day at 6,000 ppm. Bilateral 13th ribs were observed in 42/72 fetuses (18/20 litters) compared to 21/86 fetuses (12/21 litters) in controls (BRRC 1987b). Neurological effects observed in dams in the following studies are discussed in Section 2.15. Exposure of pregnant mice to 1,1,1-trichloroethane at a concentration of 2,000 ppm for 17 hours/day on GDs 12–17 resulted in significantly reduced litter weights, postnatal pup weights, overt developmental delays (pinnae detachment, incisor eruption, eye opening), and impaired performance in pups in behavioral tests (righting reflex, forelimb grip strength, negative geotaxis, inverted screen climbing) (Jones et al. 1996). There were no clinical signs of maternal toxicity and no statistically significant effects on litter size, number of live pups, ratio of male and female pups per litter, or spontaneous motor activity in pups. In another study, pregnant mice were exposed to 8,000 ppm 3 times/day for 1 hour on GDs 12–17 (Jones et al. 1996). Significantly reduced postnatal pup weight, developmental delays (pinnae detachment, incisor eruption, eye opening), and impaired performance in behavioral tests (righting reflex, forelimb grip strength, negative geotaxis, rooting reflex) were observed. Maternal weight gain was reduced during the exposure period in pregnant rats exposed to 7,000 ppm 1,1,1-trichloroethane 3 times/day for 1 hour on GDs 13–19 (Coleman et al. 1999). Developmental effects included increased mortality at birth, decreased litter weight, and significant deficits in coordination, muscle strength, and spontaneous motor activity.

No developmental effects have been found in humans after oral exposure based on epidemiology studies (Bove et al. 1995; Deane et al. 1989; Swan et al. 1989).

There were no developmental effects (pup body weight, physical maturation landmarks, motor activity, FOB results, brain measurements, neuropathology, learning capacity, task performance, or short-term memory) in the offspring of rats treated by gavage with 1,1,1-trichloroethane doses up to 750 mg/kg/day on GD 6 through lactation day 10 (Dow Chemical 1993; Maurissen et al. 1994). No significant developmental effects were observed in in rats administered up to 5.9 mg/kg/day 1,1,1-trichloroethane in

drinking water for 27 or 70 days (George et al. 1989; NTP 1988a, 1988b). In the NTP (1988a) study, 1,1,1-trichloroethane was added to the drinking water of male and female rats before mating and through lactation at doses up to 3.5 mg/kg/day. Exposure to 1,1,1-trichloroethane did not affect pup survival, pup body weight, incidence of malformed pups, or cardiovascular anomalies of any type. In the second NTP (1988b) study, rats were exposed to 1,1,1-trichloroethane in the drinking water from premating through gestation resulting in doses as high as 2.5 mg/kg/day. There were no observed adverse effects in fetuses or embryos, no effects on the incidence of external, visceral, or skeletal malformations, and no cardiovascular abnormalities.

There were no treatment-related developmental effects (pup body weights, pup survival, skeletal and visceral malformations) in the F1 or F2 generation in a multigenerational study, in which mice were exposed to 1,000 mg/kg/day 1,1,1-trichloroethane in their drinking water, with exposure beginning prior to mating and continuing through gestation and lactation (Lane et al. 1982). No maternal toxicity was observed.

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

2.18 OTHER NONCANCER

No studies were identified regarding other noncancer effects of inhalation, oral, or dermal exposure to 1,1,1-trichloroethane in humans and animals.

2.19 CANCER

Several studies examined associations between exposure to 1,1,1-trichloroethane and cancer in humans as shown in Table 2-5. The most studied cancer endpoints are cancers of the hematological and neurological systems. Of the available studies, most studies reported exposure qualitatively, with only two studies reporting quantitative exposure data (Anttila et al. 1995; McLean et al. 2014), limiting interpretation of study results. Studies evaluating associations between exposure to 1,1,1-trichloroethane and all cancer reported conflicting results, with one cohort study reporting a positive association (Anttila et al. 1995) and a second cohort reporting a negative association (Spirtas et al. 1991). Anttila et al. (1995) examined both sexes in a small Finnish cohort (n=4,004), while Spirtas et al. (1991) also evaluated both sexes but included a larger population (n=14,457). In the Anttila et al. (1995) study, urinary levels of

1,1,1-trichloroethane were 6.4 and 8.4 mg/L in males and females, respectively. Studies on associations between exposure and hematological cancers also reported conflicting results, with positive associations between 1,1,1-trichloroethane exposure and multiple myeloma observed in a case-control study (Gold et al. 2011) and multiple myeloma mortality in a large cohort study (Spirtas et al. 1991); however, no association was found between 1,1,1-trichloroethane exposure and multiple myeloma in another cohort study in Finland (Anttila et al. 1995). Findings by Anttila et al. (1995) are based on only two cases of multiple myeloma. In cohort studies, Anttila et al. (1995) found a positive association between 1,1,1-trichloroethane exposure and non-Hodgkin's lymphoma (NHL), but Spirtas et al. (1991) found no association with NHL. No association between 1,1,1-trichloroethane exposure and leukemias (in adults or in children of exposed mothers) was observed in two large case-control studies (Infante-Rivard et al. 2005; Talibov et al. 2017) or cohort studies (Anttila et al. 1995; Spirtas et al. 1991). Limitations of the cohort studies include exposure to multiple chemicals and lack of quantitative exposure monitoring (air concentrations or biomarker); most exposure estimates were qualitatively described using job coding matrices and/or industrial hygiene records. Evaluation of 1,1,1-trichloroethane exposure and cancers of the nervous system show primarily no association (Heineman et al. 1994; Neta et al. 2012; McLean et al. 2014; Mulla 1996); however, Anttila et al. (1995) found a positive association between 1,1,1-trichloroethane and cancers of the central nervous system. A positive association was found between 1,1,1-trichloroethane exposure and stomach cancer in a cohort study (Anttila et al. 1995); however, no association with cancers of the stomach or esophagus were observed in a larger cohort (Rohr Indus Inc. 1986, 1987). Studies evaluating cancer of the reproductive organs were limited to a small cohort; Anttila et al. (1995) found a positive association between 1,1,1-trichloroethane exposure and cervical cancer, but no association was observed with prostate cancer. No associations were observed between 1,1,1-trichloroethane exposure and kidney cancer in a single case-control study (Purdue et al. 2017).

Table 2-5. Summary of Epidemiological Studies Evaluating Possible Associations Between 1,1,1-Trichloroethane Exposure and Risk of Selected Cancer Types

Reference, study type, and population	Exposure	Cancer type	Result
All cancer			
Anttila et al. 1995 Cohort, 2,050 males, 1,924 females, Finland	Urinary 1,1,1-trichloroethane Men: mean 6.4 mg/L Women: mean 8.4 mg/L	All cancer	↑
Spirtas et al. 1991 Cohort, 14,457 Airforce base workers, Utah, United States	NR	All cancer mortality	↓

Table 2-5. Summary of Epidemiological Studies Evaluating Possible Associations Between 1,1,1-Trichloroethane Exposure and Risk of Selected Cancer Types

Reference, study type, and population	Exposure	Cancer type	Result
Hematological cancer			
Anttila et al. 1995 Cohort, 2,050 males, 1,924 females, Finland	Urinary 1,1,1-trichloroethane Men: 6.4 mg/L Women: 8.4 mgl/L	Multiple myeloma	↔
		Leukemia	↔
		NHL	↑
Gold et al. 2011 Case-control, 181 cases, 481 controls, SEER study Washington and Michigan, United States	Subjective (ever exposed versus unexposed)	Multiple myeloma	↑
Infante-Rivard et al. 2005 Case-control, 790 cases, 790 controls, Canada	Maternal exposure classified as no exposure and any exposure	Acute lymphoblastic leukemia	↔
Spirtas et al. 1991 Cohort, 14,457 Airforce base workers**,** Utah, United States	NR	Multiple myeloma mortality	↑
		NHL mortality	↔
		Leukemia mortality	↔
Talibov et al. 2017 Case-control, 20,615 cases, 103,075 controls, Nordic countries	Cumulative exposure stratified in tertiles (T) T1: ≤5.6 ppm-years T2: 5.6–12.9 ppm-years T3: >12.9 ppm-years	Leukemia (CLL)	↔
Nervous system cancer			
Anttila et al. 1995 Cohort, 2,050 males, 1,924 females, Finland	Urinary 1,1,1-trichloroethane Men: 6.4 mg/L Women: 8.4 mgl/L	Cancer of the central nervous system	↑
Heineman et al. 1994 Case-control, 741 cases, 714 controls, Louisiana, New Jersey, and Pennsylvania, United States	Qualitative exposure classified as no exposure, low, medium, and high	Astrocytic brain cancer	↔
McLean et al. 2014 Case-control, 1,906 cases, 5,565 controls, New Zealand	Mean cumulative exposure: Cases: 188 ppm Controls: 458 ppm	Meningioma	↔
Mulla 1996 Cross-sectional, 26 counties Florida, United States	NA	Brain tumors	↔
Neta et al. 2012 Case-control, 489 cases, 799 controls, Arizona, Mississippi, and Pennsylvania, United States	Classified as unexposed, possible exposure, and probably exposure	Glioma	↔
		Meningioma	↔

Table 2-5. Summary of Epidemiological Studies Evaluating Possible Associations Between 1,1,1-Trichloroethane Exposure and Risk of Selected Cancer Types

Reference, study type, and population	Exposure	Cancer type	Result
Kidney cancer			
Purdue et al. 2017 Case-control, 1,217 cases, 1,235 controls, Michigan and Illinois, United States	Stratified by probability of exposure: 0, <10, 10–49, 50–89, and ≥90%	Kidney cancer	↔
Gastrointestinal cancer			
Anttila et al. 1995 Cohort, 2,050 males, 1,924 females, Finland	Urinary 1,1,1-trichloroethane Men: 6.4 mg/L Women: 8.4 mgl/L	Stomach	↑
Rohr Indus Inc. 1986, 1987 Cohort, 14,067 workers (85% male, 15% female)	Ever versus never exposed estimated by job matrix	Esophageal or stomach cancer	↔
Reproductive organ cancer			
Anttila et al. 1995 Cohort, 2,050 males, 1,924 females, Finland	Urinary 1,1,1-trichloroethane Men: 6.4 mg/L Women: 8.4 mgl/L	Cervical	↑
		Prostate	↔

↑ = increase; ↓ = decrease; ↔ = no change; CLL = chronic lymphocytic leukemia; NA = not applicable; NHL = non-Hodgkin's lymphoma; NR = not reported; T = tertile

Cancer studies in animals exposed to 1,1,1-trichloroethane via inhalation were limited to two 2-year studies that evaluated necropsy and histopathology in all animals (Ohnishi et al. 2013; Quast et al. 1988). Multiple carcinogenic effects were observed in the chronic-duration study by Ohnishi et al. (2013), in which rats were exposed to 0, 200, 797, or 3,181 ppm and mice were exposed to 0, 201, 801, or 3,204 ppm for 6 hours/day, 5 days/week, for 104 weeks. Cancers of the respiratory tract were observed in both species. In male rats, bronchioloalveolar adenomas showed a positive trend with incidences of 0/50, 1/50, 7/50, 4/50, at 0, 200, 797, or 3,181 ppm, respectively; however, female rats showed no carcinogenic effects in the same study. In mice (both sexes), there were increased trends for bronchioloalveolar carcinomas and combined bronchioloalveolar adenomas and carcinomas in the lung. At 3,204 ppm, 7/49 female mice had combined bronchioloalveolar adenomas and carcinomas in the lung, compared with 1/50 in controls. In male F344 rats exposed to 3,181 ppm 1,1,1-trichloroethane, incidence of mesothelioma in the peritoneum was increased (16/50 compared to 1/50 in controls) and a positive trend was also observed. Mesothelioma in the peritoneum was not observed in female rats or in mice of either sex. There were no other cancer types reported in rats.

Mice exhibited additional cancer types compared to rats (Ohnishi et al. 2013). Males exhibited a positive trend in hepatocellular adenoma incidence, females exhibited a dose-dependent increase that was statistically significant in all exposed groups (2/50, 9/48, 14/50, and 19/49 at 0, 200, 797, and 3,181 ppm, respectively). Female mice also exhibited increased incidences of combined hepatocellular adenomas and carcinomas (4/50, 10/48, 16/50, 20/49, at 0, 200, 797, and 3,181 ppm, respectively), significant at concentrations of ≥797 ppm. The incidences in all exposure groups exceeded the maximum historical control values. Male mice appear to be more sensitive as the following cancer types were observed only in males. There was an increased trend for Harderian gland adenoma, with significantly increased incidence at 3,204 ppm (8/50 compared with 1/50 in controls). There was also an increased trend for malignant lymphoma of the spleen; while not statistically significant, it did exceed the maximum tumor incidence in the historical control data.

In contrast to findings in the Ohnishi et al. (2013) study, the 2-year carcinogenicity study by Quast et al. (1988) found no carcinogenic effects in rats or mice exposed to concentrations of 150–1,500 ppm 1,1,1-trichloroethane.

Isacson et al. (1985) found no association between of 1,1,1-trichloroethane in drinking water and the incidence of bladder, colon, lung, rectum, breast, or prostate cancer in people over 55 years of age. No other studies were identified regarding other cancer effects of oral exposure to 1,1,1-trichloroethane in humans.

Oral cancer studies in animals were limited to two chronic-duration studies that evaluated a comprehensive set of endpoints (Maltoni et al. 1986; NCI 1977), with conflicting results. Maltoni et al. (1986) conducted a 104-week carcinogenicity study that found an increase in the total incidence of rats with leukemias, with 13/80 (9/40 males and 4/40 females) in treated rats compared to 4/100 (3/50 males and 1/50 females) in vehicle controls. NCI (1977) conducted a 78-week (reduced duration due to early mortality) carcinogenicity bioassay, including necropsy and histological evaluation in all animals, for 1,1,1-trichloroethane in rats and mice. Gavage doses were 750 or 1,500 mg/kg/day in rats and 2,807 or 5,615 mg/kg/day in mice. The incidence and type of neoplasms observed in treated animals were comparable to untreated controls (vehicle controls were not used). There was a significant dose-related decrease in survival with a mortality rate of 100% for male rats, 96–98% for female rats, 70–78% for male mice, and 54–74% for female mice. Because the high rate of early mortality may have lowered the incidence of late-appearing tumors, the study authors did not consider this study an adequate test of 1,1,1-trichloroethane carcinogenicity in either species.

No studies were identified regarding cancer effects of dermal exposure to 1,1,1-trichloroethane in humans or animals.

The Department of Health and Human Services (NTP 2021) has not classified the carcinogenicity of 1,1,1-trichloroethane. The International Agency for Research on Cancer (IARC) has classified 1,1,1-trichloroethane as Group 2A, *probably carcinogenic to humans*, based on limited evidence for cancer in humans including positive associations with multiple myeloma, and sufficient evidence for cancer in experimental animals (IARC 2022). The EPA (2007) determined that there was inadequate information to assess carcinogenic potential of 1,1,1-trichloroethane.

2.20 GENOTOXICITY

Results of *in vivo* genotoxicity studies are summarized in Table 2-6. *In vivo* tests were negative for Basc test and mitotic recombination test in *Drosophila melanogaster,* and micronuclei tests and DNA damage tests in mice (see Table 2-6). Weakly positive results were reported for DNA adducts in mouse liver (Turina et al. 1986). No effects were observed with 1,1,1-trichloroethane in an initiation-promotion assay (Milman et al. 1988)

Table 2-6. Genotoxicity of 1,1,1-Trichloroethane *In Vivo*

Species (test system)	Endpoint	Results	Reference
Drosophila melanogaster	Sex linked recessive lethal mutations	–	Gocke et al. 1981
D. melanogaster	Mitotic recombination	–	Vogel and Nivard 1993
Mouse erythrocytes	Micronucleus test	–	Tsuchimoto and Matter 1981
Mouse bone marrow	Micronucleus test	–	Gocke et al. 1981; Kataz et al. 1981; Mackay et al. 1987; Salamone et al. 1981
Mouse liver	DNA adducts	(+)	Turina et al. 1986
Mouse liver	DNA unwinding	–	Taningher et al. 1991
Rat liver	DNA synthesis	+	Truffert et al. 1977

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

Results of genotoxicity studies *in vitro* are summarized in Table 2-7. While the results of *in vitro* mutation testing were mostly negative, those tests that employed a system designed to minimize volatilization, likely preserving or prolonging exposure, reported positive results in mutagenic assays in

Salmonella typhimurium (Gocke et al. 1981; Nestmann et al. 1980, 1984; Simmon et al. 1977). These results suggest that exposure conditions may play a role in mutagenicity.

Table 2-7. Genotoxicity of 1,1,1-Trichloroethane *In Vitro*

Species (test system)	Endpoint	Results		Reference
		With activation	Without activation	
Prokaryotic organisms				
Salmonella typhimurium on plates or in liquid	Reverse mutation	–	–	Baker and Bonin 1981; Brooks and Dean 1981; Falck et al. 1985; Ichinotsubo et al. 1981; Legault et al. 1994; MacDonald 1981; Milman et al. 1988; Nagao and Takahashi 1981; Nestmann et al. 1980; Quillardet et al. 1985; Richold and Jones 1981; Rowland and Severn 1981; Simmon and Shepherd 1981; Suovaniemi et al. 1985; Trueman 1981; Venitt and Crofton-Sleigh 1981
S. typhimurium on plates in desiccator	Reverse mutation	+	+	Gocke et al. 1981; Nestmann et al. 1980, 1984; Simmon et al. 1977
S. typhimurium	Fluctuation	–	–	Gatehouse 1981; Hubbard et al. 1981
S. typhimurium	Forward mutation	–	ND	Skopek et al. 1981
S. typhimurium	Ara test	–	–	Roldan-Arjona et al. 1991
S. typhimurium	*umu* test	–	–	Nakamura et al. 1987; Ono et al. 1991
S. typhimurium	Rec-assay for DNA repair	–	–	Kada 1981
Escherichia coli	Reverse mutation	–	–	Matsushima et al. 1981
E. coli	Differential killing	–	–	Green 1981; Tweats 1981
E. coli	Lambda prophage induction	–	–	Thomson 1981
E. coli	Gene induction	–	ND	Quillardet et al. 1985
E. coli	Growth inhibition	(+)	–	Rosenkranz et al. 1981
E. coli	DNA damage	ND	–	Legault et al. 1994
Vibrio fischeri	DNA damage	ND	–	Legault et al. 1994
Eukaryotic organisms: fungi				
Schizosaccharo-myces pombe	Forward mutation	–	–	Loprieno 1981
Aspergillus nidulans	Forward mutation	ND	–	Crebelli and Carere 1988
A. nidulans	Mitotic aneuploidy	ND	–	Crebelli and Carere 1988; Crebelli et al. 1988

Table 2-7. Genotoxicity of 1,1,1-Trichloroethane *In Vitro*

Species (test system)	Endpoint	Results		Reference
		With activation	Without activation	
A. nidulans	Mitotic crossing over	ND	–	Crebelli and Carere 1988
Saccharomyces cerevisiae	Gene deletions	ND	(+)	Brennan and Schiestl 1998
S. cerevisiae	Reversion	–	–	Mehta and von Borstel 1981
S. cerevisiae	Mitotic aneuploidy	ND	–	Whittaker et al. 1990
S. cerevisiae	Mitotic aneuploidy	–	ND	Parry and Sharp 1981
S. cerevisiae	Mitotic crossing over	–	–	Kassinova et al. 1981
S. cerevisiae	Mitotic gene conversion	–	–	Jagannath et al. 1981; Sharp and Parry 1981a; Zimmermann and Scheel 1981
S. cerevisiae	DNA repair	–	–	Brennan and Schiestl 1998; Sharp and Parry 1981b
Mammalian cells				
HeLa cells	Unscheduled DNA synthesis	–	–	Martin and McDermid 1981
Rat hepatocytes	Unscheduled DNA synthesis	ND	–	Althaus et al. 1982; Milman et al. 1988; Williams et al. 1989
Rat hepatocytes	DNA repair	ND	–	Milman et al. 1988
Mouse hepatocytes	DNA repair	ND	+	Milman et al. 1988
Rat hepatocytes	Degranulation of endoplasmic reticulum	ND	+	Fey et al. 1981
Human lymphoblasts	Gene locus mutation	ND	–	Penman and Crespi 1987
L5178Y mouse lymphoma cells	Forward mutation	±	–	Myhr and Caspary 1988
L5178Y mouse lymphoma cells	Chromosomal aberrations	–	–	Mitchell et al. 1988
Chinese hamster ovary cells	Chromosomal aberrations	(+)	+	Galloway et al. 1987
Chinese hamster ovary cells	Sister chromatid exchange	–	ND	Perry and Thomson 1981
Chinese hamster ovary cells	Sister chromatid exchange	±	–	Galloway et al. 1987
Human peripheral lymphocytes	Sister chromatid exchange	ND	–	Lindahl-Kiessling et al. 1989
Hamster kidney cells	Cell transformation	–	ND	Styles 1981
Rat embryo cells F1706	Cell transformation	+	+	Daniel and Dehnel 1981
Rat embryo cells F1706	Cell transformation	ND	+	Price et al. 1978
Hamster embryo cells	Cell transformation	ND	+	Hatch et al. 1983; Hatch et al. 1982

Table 2-7. Genotoxicity of 1,1,1-Trichloroethane *In Vitro*

Species (test system)	Endpoint	Results		Reference
		With activation	Without activation	
Mice BALB/c-3T3 cells	Cell transformation	ND	+	Milman et al. 1988; Tu et al. 1985
Calf thymus	DNA Binding	–	ND	DiRenzo et al. 1982

= negative; + = positive; (+) = weakly positive; ± = equivocal; DNA = deoxyribonucleic acid; ND = no data

Chromosomal aberrations were reported in Chinese hamster ovary cells *in vitro* (Galloway et al. 1987) but not in mouse lymphoma cells (Mitchell et al. 1988). Positive or weakly positive results were reported in *in vitro* assays for DNA repair in mouse and rat hepatocytes (Milman et al. 1988).

Positive results *in vitro* were reported for degranulation of endoplasmic reticulum, a measure of the ability of a compound to displace polysomes from endoplasmic reticulum in rat hepatocytes (Fey et al. 1981) and for promoting cell transformation, a process believed to be similar to neoplastic transformation *in vivo*, in rat embryo cells, hamster embryo cells, baby hamster kidney cells, and mouse BALB/c-3T3 cells (Daniel and Dehnel 1981; Hatch et al. 1982, 1983; Milman et al. 1988; Price et al. 1978; Tu et al. 1985).

Mixed results in mutagenicity studies suggest that the volatility of 1,1,1-trichloroethane needs to be considered in exposure during mutagenicity assays. Positive results in chromosomal aberrations were observed in a Chinese hamster ovary cell assay only. 1,1,1-Trichloroethane was positive in most mammalian cell transformation assays.

CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

3.1 TOXICOKINETICS

Information on the toxicokinetics of 1,1,1-trichloroethane is available from a small number of human studies and several animal studies; a brief summary of findings is provided below.

- 1,1,1-Trichloroethane is rapidly and efficiently absorbed by the lung, skin (under conditions to prevent evaporation), and gastrointestinal tract of humans and animals. Rapid and passive diffusion of 1,1,1-trichloroethane across cell membranes is facilitated by the chemical's lipophilicity and low molecular weight.

- Animal studies have demonstrated that, once absorbed, 1,1,1-trichloroethane is distributed by the blood to tissues and organs throughout the body, including to developing fetuses, with preferential distribution to fatty tissues.

- 1,1,1-Trichloroethane is metabolized oxidatively, at low rates, to trichloroethanol and trichloroacetic acid by the cytochrome P-450 mixed-function oxidase system. These metabolites are excreted in the urine, and other minor metabolites (carbon dioxide [CO_2] and acetylene) are excreted in expired air. Experiments with animals and humans have demonstrated that only small fractions of absorbed 1,1,1-trichloroethane doses (<10%) are metabolized, regardless of the route of exposure.

- The predominant pathway of elimination of 1,1,1-trichloroethane in humans and animals, regardless of route of exposure, is exhalation of the unchanged compound. When exposure ceases, the compound is rapidly cleared from the body. In animal studies, only trace amounts of the compound remain in tissues within days of the termination of short-term exposure.

3.1.1 Absorption

Data from experiments in which humans were exposed for short periods to 1,1,1-trichloroethane vapors indicate that the compound is rapidly and extensively absorbed by the respiratory system. 1,1,1-Trichloroethane was detected in the arterial blood of men within ≈10 seconds after exposure to 250 or 350 ppm (Astrand et al. 1973). When subjects held single breaths of air containing radiolabeled 1,1,1-trichloroethane for 15–40 seconds, alveolar concentrations decreased to between 10 and 20% of the initial concentrations, indicating extensive absorption upon initial exposure (Morgan et al. 1972a, 1972b). Human studies on 1,1,1-trichloroethane use exhaled breath, blood, or urine as surrogates for estimating the exposure dose of 1,1,1-trichlorethane. Droz et al. (1988) exposed volunteers to 1,1,1-trichloroethane that was detected in breath for up to15 hours postexposure after inhalation of 200 ppm 1,1,1-trichloroethane. Nagatoshi et al. (1994) concluded that worker exposure was extremely small in factories that

exercised proper control over exposure to 1,1,1-trichloroethane and other solvents. Nolan et al. (1984) used both blood and expired air concentrations of 1,1,1-trichloroethane to validate absorption of the chemical via inhalation exposure after a 6-hour exposure. Correlations between absorption via inhalation exposure to 1,1,1-trichloroethane and blood concentrations have been observed in numerous studies (Gill et al. 1991; Hajimiragha et al. 1986; Monster and Houtkooper 1979; Tay et al. 1995).

The extent of absorption of inhaled 1,1,1-trichloroethane decreases with continued exposure to the compound, as concentrations in alveolar air, blood, and tissues attain near equilibrium or steady state. Average lung retentions of 25–30% were measured in humans exposed to 35–350 ppm for 4–6 hours (i.e., the concentration of 1,1,1-trichloroethane in expired air after 4–6 hours of exposure equaled 70–75% of the inspired concentration) (Monster et al. 1979; Nolan et al. 1984). The concentration in blood increased rapidly in the first 1.5 hours, which was 90% of the peak of the systematic uptake (Nolan et al. 1984). Physical exercise during 0.5–4-hour exposures increased systemic absorption of 1,1,1-trichloroethane, due to increased alveolar ventilation and cardiac output (Astrand et al. 1973; Monster et al. 1979). A physiologically-based pharmacokinetic (PBPK) model developed by Laparé et al. (1995) suggested that a 10-minute workload increases alveolar uptake of 1,1,1-trichloroethane by 12%. While steady-state levels in blood are approached within the first hours after exposure begins (Astrand et al. 1973; Monster et al. 1979; Nolan et al. 1984), Nolan et al. (1984) predicted, using a physiologically-based kinetic model, that 12 consecutive 6-hour daily exposures (presumably to concentrations of 350 ppm) would be required for 1,1,1-trichloroethane in body tissues to reach 95% of steady state. A more recently developed physiological kinetic model predicted that steady-state venous blood concentrations of 1,1,1-trichloroethane would be achieved within 14 days after exposure levels in the range of 10–5,000 ppm based on the Reitz et al. (1988) model (EPA 2006a; Lu et al. 2008). These studies also predicted that 94% of steady-state blood concentration would be reached within 4 days and 98% of steady-state would be reached within 7 days. Absorption is expected to be relatively low after steady state is reached because the initial extensive absorption of 1,1,1-trichloroethane is the result of blood and tissue loading, which in turn is affected by respective blood:air and tissue:blood partition coefficients, tissue volumes and blood flows, and low metabolism (Johns et al. 2006; Reitz et al. 1988). Blood:air partition coefficients for humans, rats, and mice were 2.53, 5.76, and 10.8, respectively (Reitz et al. 1988), meaning that small rodents will experience greater systemic uptake than humans, with mice receiving the highest dose. Mice also have the highest respiratory and circulatory rates, two additional factors that significantly influence systemic absorption of 1,1,1-trichloroethane. 1,1,1-Trichloroethane is poorly metabolized in humans and animals (see Section 3.1.3).

Animal experiments provide supporting evidence that inhaled 1,1,1-trichloroethane is rapidly and extensively absorbed and that the absorption, during short-term exposures, is influenced by ventilation rate (Schumann et al. 1982; Dallas et al. 1989; Gargas et al. 1986; Warren et al. 1998; You and Dallas 2000). In rats exposed to 50 or 500 ppm, the percentage uptake decreased from ~80% at the onset of exposure to ~50% after 2 hours post-exposure. 1,1,1-Trichloroethane was detected in arterial blood within 2 minutes of the onset of exposure and approached steady-state concentrations within 2 hours (Dallas et al. 1989). In rats exposed to 1,000–5,000 ppm, 1,1,1-trichloroethane was rapidly absorbed by the lungs within 10 minutes of inhalation exposure and achieved equilibrium in the blood and brain within 40 minutes during a 100-minute inhalation exposure to 1,000 or 2,000 ppm (Warren et al. 1998). In mice and rats exposed to 3,500 and 5,000 ppm, 1,1,1-trichloroethane concentrations in blood increased rapidly during the first 10 minutes, and the concentrations measured after an hour were >90% of the concentrations measured after 2 hours (You and Dallas 1998). Concentrations at steady state were achieved also within 2 hours (You and Dallas 1998). The blood 1,1,1-trichloroethane concentration in mice increased more rapidly than that in rats for the first 10 minutes and was significantly higher in mice at 1- and 2-hours post-exposure to either concentration administered (You and Dallas 1998). In anesthetized dogs under regulated respiration conditions, 1,1,1-trichloroethane was detected in arterial blood within 2 minutes of the onset of exposure to 700, 1,500, or 3,000 ppm. Arterial blood concentrations approached steady-state levels within 1 hour at 700 ppm, but not at 1,500 or 3,000 ppm; absorption increased with increases in pulmonary ventilation rate (Hobara et al. 1982, 1983a, 1983b).

Data regarding the rate or extent of absorption of ingested 1,1,1-trichloroethane in humans are not available, but based on extensive animal data, it is anticipated that oral absorption of 1,1,1-trichloroethane will be extensive in humans. Animal experiments indicate that 1,1,1-trichloroethane is rapidly and completely absorbed by the gastrointestinal tract. Maximum levels of 1,1,1-trichloroethane in venous blood of rats were detected within 7–15 minutes of gavage administration of a 6–48-mg/kg dose in water (Mortuza et al. 2018; Reitz et al. 1988). In experiments in which rats were given 8-hour free access to drinking water containing [2–14C]-labeled 1,1,1-trichloroethane, radioactivity in expired air, urine, and selected tissues (assayed 56 hours following cessation of access to the labeled water) represented 95.2% of the average dose of 116 mg/kg, indicating nearly complete absorption of the administered dose (Reitz et al. 1988). In experiments with rats and mice given single gavage doses of radiolabeled 1,1,1-trichloroethane in vegetable oil ranging from 100 to 3,000 mg/kg, dose-recovery in expired air ranged from 90 to 97% (RTI 1987). After administration of 22.5–30 mmol/kg oral dose of 1,1,1-trichloroethane in rats and mice, 88–98% of doses were recovered through expired air and urine in 48 hours (Mitoma et al. 1985).

Mortuza et al. (2018) estimated a high portion of systemic uptake after doses of 6 and 48 mg/kg of aqueous emulsions of 1,1,1-trichloroethane by gavage and gastric infusion, respectively, over 2 hours in rats. Peak blood levels were obtained within 8 minutes after 1,1,1-trichloroethane administration by gavage, while blood levels progressively rose when the chemical was infused into the stomach, exceeding levels in the gavage groups after 60–80 minutes (Mortuza et al. 2018).

Absorption from the gastrointestinal tract is more rapid for 1,1,1-trichloroethane given in water than in vegetable oils, because the oils act as a reservoir for the chemical in the gut, so that most of the chemical remains in the oil in the gut until the oil is digested and absorbed (Reitz et al. 1988; RTI 1987).

1,1,1-Trichloroethane is absorbed through human skin. Absorption of 1,1,1-trichloroethane through skin is dependent on phase of media, exposure conditions (i.e., immersion or topical application), skin type, and size of exposed area. Studies involving dermal absorption showed rapid absorption related to the type or condition of skin exposed, duration of exposure, and exposure concentration (Aitio et al. 1984; Poet et al. 2000; Stewart and Dodd 1964). Other studies where exposure is via percutaneous absorption of solvent vapors have also been conducted and found similar rapid absorption occurring (Giardino et al. 1999; Riihimäki and Pfäffli 1978; Wallace et al. 1989). The compound was detected in alveolar air of human volunteers during 30-minute skin absorption experiments with concentration ranges of 0.1–1.0 ppm after thumb immersion, 21.5 ppm after hand immersion, and 0.65 ppm after hand topical application to the undiluted compound (Stewart and Dodd 1964). 1,1,1-Trichloroethane concentrations in blood and alveolar air were 3–4 μg/mL and 2–5 ppm, respectively, immediately following the last of three daily 2-hour exposures of 12.5-cm^2 areas of covered forearm skin in application experiments (Fukabori et al. 1977). A dermal absorption rate of 56 nmol 1,1,1-trichloroethane/minute/cm^2 was calculated for human subjects exposed for 3 minutes to liquid 1,1,1-trichloroethane (neat) on a 3-cm^2 area of forearm skin (Kezic et al. 2001). Less than 0.2% of the available 1,1,1-trichloroethane was absorbed (with an estimated dermal absorption rate ranging from 0.0057 to 0.0069 cm/hour) in humans after a 2-hour hand immersion in a 0.1% (1 g/kg) water solution of 1,1,1-trichloroethane (Poet et al. 2000). The human dermal absorption rate from a 0.75% soil solution was approximately 1/3 of that from water, with an estimated rate of 0.002±0.0005 cm/hour (Poet et al. 2000). Pre-hydration of skin for 2 hours prior to exposure resulted in 2 orders of magnitude higher estimated absorption (0.528 cm/hour), and a greater mass (377 mg) of the amount absorbed (Poet et al. 2000). Another human study on percutaneous absorption of 1,1,1-trichloroethane from aqueous solutions reported 14.9% dermal uptake in volunteers following a 1-hour immersion of their hand and forearm into water containing 100 μg/L 1,1,1-trichloroethane, and estimated a dermal permeability coefficient of 0.167 cm/hour (Fan et al. 2007). Dermal

absorption was 45.7 nmol/minute/cm^2 in mice after 2.92-cm^2 areas of skin were exposed to undiluted compound for 15 minutes under occluded conditions to prevent evaporative loss (Tsuruta 1975). In rats, ≈30% of a 2-mL volume of undiluted 1,1,1-trichloroethane was absorbed by a 3.1-cm^2 area of skin in 24 hours under occluded conditions (Morgan et al. 1991).

Following dermal exposure of rats to 0.1% 1,1,1-trichloroethane in 5 mL of water (5 cm^2 surface area exposed), peak exhaled breath concentrations (Cmax) of ~1,600 ppb were obtained within 1 hour (Poet et al. 2000). The extent of the absorption was dependent on the exposure duration, as 61 and 87% of the applied dose was absorbed after 4 hours and 8 hours of exposure, respectively (Poet et al. 2000). Rat dermal absorption of 0.15±0.006 cm/hour (33%) from non-occluded soil was half of the absorption rate as measured from water (Poet et al. 2000).

Skin provides an excellent barrier against dermal absorption of 1,1,1-trichloroethane vapors. Negligible amounts of chemical vapors are absorbed through heated and moist skin in a dose-dependent manner. After exposure to vapor concentrations ranging from ~1,200 to 4,800 mg/m^3, 25–260 µg/m^3 1,1,1-trichloroethane was exhaled in a linearly dose-dependent manner (Giardino et al. 1999). Dermal uptake from the whole body was approximately 0.1%, while dermal uptake through a forearm and hand, which is 30% of the total body surface area, was approximately 0.031% (Giardino et al. 1999; Riihimäki and Pfäffli 1978). An absorption rate into skin of 0.021 cm/hour and a maximum absorption rate into the blood of 0.005 nmol/hour were reported for volunteers whose forearm and hand were exposed to approximately 38,000 ppm 1,1,1-trichloroethane vapors for 20 minutes (Kezic et al. 2000).

3.1.2 Distribution

No studies were identified regarding the distribution of 1,1,1-trichloroethane to human tissues after inhalation exposure. Nevertheless, 30 autopsies revealed detectable levels of the compound in subcutaneous and renal fat, liver, lung, and muscle (Alles et al. 1988). Additionally, most of absorbed 1,1,1-trichloroethane in humans is rapidly excreted in exhaled air as the unmetabolized parent compound (Caplan et al. 1976; Gamberale and Hultengren 1973).

Animal studies indicate that inhaled 1,1,1-trichloroethane is distributed by the blood to tissues and organs throughout the body, with preferential distribution to fatty tissues. 1,1,1-Trichloroethane is rapidly cleared from tissues after exposure ceases (Holmberg et al. 1977; Schumann et al. 1982; Takahara 1986a). Concentrations of 1,1,1-trichloroethane were higher in the liver than in the blood, kidneys, and brain of

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

No studies were identified regarding the distribution of 1,1,1-trichloroethane to human tissue after oral exposure to the compound. Ingested 1,1,1-trichloroethane, however, is probably widely distributed among tissues based on results of animal studies. Distribution of 1,1,1-trichloroethane to tissues will be governed by several factors, including tissue blood flow rate, tissue volume, and tissue:blood partition coefficient, the latter factor being probably the most important. Following gavage administration of 1,1,1-trichloroethane in vegetable oil to rats (100, 300, or 1,000 mg/kg) or mice (300, 1,000, or 3,000 mg/kg), the compound was distributed to tissues throughout the body, with preferential accumulation in fatty tissues (RTI 1987). After a 6 mg/kg gavage-administered dose of an aqueous emulsion of 1,1,1-trichloroethane in rats, the chemical was most rapidly distributed to the liver, with levels in the organ peaking within 5 minutes of administration (Mortuza et al. 2018). Peak levels in blood and tissues were observed approximately 15 minutes post-exposure (Mortuza et al. 2018). The liver exhibited a 2–3-fold higher burden of 1,1,1-trichloroethane than all other non-adipose tissues throughout the 18-hour monitoring period (Mortuza et al. 2018). As 1,1,1-trichloroethane is lipophilic, it heavily accumulated in adipose tissue in rats with a peak concentration 10-fold higher than the peak concentration in the liver, which had the next highest peak concentration (Mortuza et al. 2018). Adipose tissue also exhibited delayed clearance compared with other tissues in the rat (Hajimiragha et al. 1986; Meredith et al. 1989; Monster et al. 1979; Mortuza et al. 2018). Consistent with the conclusion that 1,1,1-trichloroethane is stored and gradually released after repeated exposures in Seki et al. (1975).

3.1.3 Metabolism

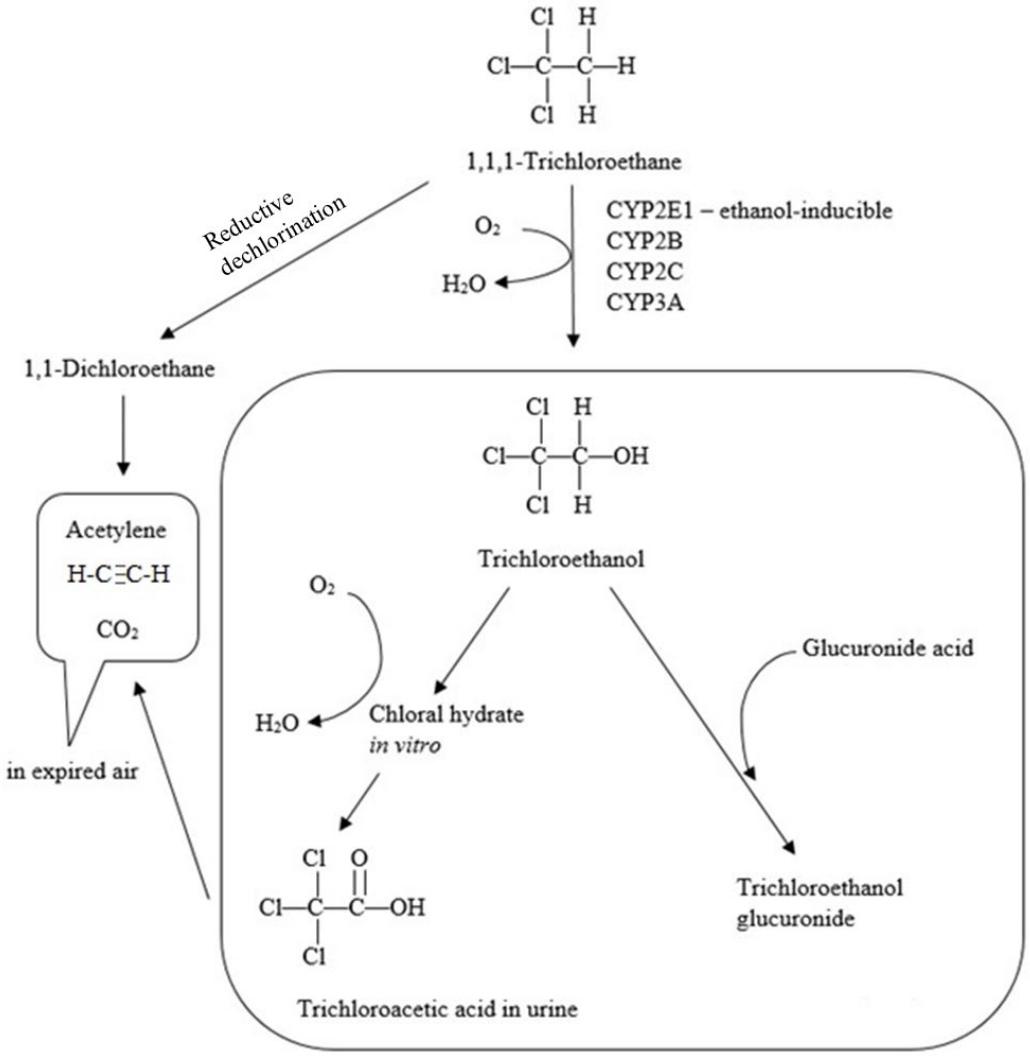
Metabolism appears to play a relatively minor role in the overall disposition of 1,1,1-trichloroethane in humans and animals. Only a small fraction of the absorbed dose (<10%) is metabolized; a large fraction of the absorbed dose is excreted unchanged in exhaled air, regardless of the exposure route. Of the 10% of 1,1,1-trichloroethane that is absorbed, 2–5% is eliminated as trichloroethanol (half-life of 10–27 hours) and 1–2% as trichloroacetic acid (half-life of 70–85 hours) in urine, representing a minor elimination pathway (Humbert and Fernandez 1976; Imbriani et al. 1988; Monster 1986). Human studies have demonstrated that trichloroethanol and trichloroacetic acid are the primary metabolites, with trichloroethanol being the more abundant one of the two (Berode et al. 1990; Kawai et al. 1991; Nolan et al. 1984; Pedrozo and Siqueira 1996; Tomicic et al. 2011).

In humans exposed to 70 or 145 ppm 1,1,1-trichloroethane in air for 4 hours, an estimated 60–80% of the absorbed compound was excreted unchanged in exhaled breath (Monster et al. 1979). Metabolites in urine, trichloroethanol and trichloroacetic acid, collected for 70 hours postexposure represented approximately 2 and 0.5%, respectively, of the 1,1,1-trichloroethane initially absorbed. In humans exposed to 35 or 350 ppm for 6 hours, >91% of absorbed 1,1,1-trichloroethane was excreted unchanged by the lungs, 5–6% was metabolized and excreted as trichloroethanol and trichloroacetic acid, and <1% remained in the body after 9 days (Nolan et al. 1984). The average apparent metabolic clearance of 1,1,1-trichloroethane was estimated at 18.05 mL/minute (Johns et al. 2006).

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

Analysis of urine following human and animal exposure to 1,1,1-trichloroethane identified trichloroethanol, trichloroethanol glucuronide, and trichloroacetic acid as major metabolites of 1,1,1-trichloroethane; CO_2, identified in exhaled breath, is the other major metabolite (Kawai et al. 1991; Mitoma et al. 1985; Monster et al. 1979; Nolan et al. 1984; Reitz et al. 1988; Schumann et al. 1982). Figure 3-1 illustrates a general metabolic scheme for 1,1,1-trichloroethane. The initial oxidation step is thought to be catalyzed by the microsomal cytochrome P-450 mixed-function oxidase system. *In vitro* reaction mixtures containing rat hepatic microsomes and NADPH oxidize 1,1,1-trichloroethane to trichloroethanol.

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



1,1,1-Trichloroethane metabolism significantly increased when microsomes from rats pretreated with phenobarbital, an inducer of certain isozymes of cytochrome P-450, were used. This finding provides supporting evidence of the involvement of this enzyme system in the metabolism, albeit limited, of 1,1,1-trichloroethane (Ivanetich and Van den Honert 1981; Koizumi et al. 1983).

The pathway for conversion of trichloroethanol to trichloroacetic acid presumably involves the intermediate formation of chloral hydrate and may involve alcohol and aldehyde dehydrogenases or cytochrome P-450 mixed-function oxidases (Casciola and Ivanetich 1984; Ivanetich and Van den Honert 1981). Although trichloroacetic acid or chloral hydrate were not detected as *in vitro* metabolic products of 1,1,1-trichloroethane with rat hepatic microsomal cytochrome P-450 preparations (Ivanetich and Van den Honert 1981; Koizumi et al. 1983), *in vitro* production of chloral hydrate from 1,1,1-trichloroethane was demonstrated in reaction mixtures containing rat nuclei cytochrome P-450 preparations (Casciola and Ivanetich 1984). Guengerich et al. (1991) concluded that metabolism of 1,1,1-trichloroethane to trichloroethanol occurs primarily by human cytochrome P-450 2E1 (CYP2E1), which is supported by two additional studies (Berode et al. 1990; Johns et al. 2006) that provide indirect evidence for the function of various cytochrome P-450 enzymes in 1,1,1-trichloroethane oxidation. These studies correlated metabolism of 1,1,1-trichloroethane with that of other CYP2E1 substrates and showed that metabolism of 1,1,1-trichloroethane is increased by ethanol consumption. 1,1,1-Trichloroethane is oxidized by one of several cytochrome P-450 enzymes to form trichloroethanol, which subsequently undergoes either oxidation to trichloroacetic acid or glucuronidation to form the corresponding trichloroethanol glucuronide conjugate, TCOG. Both metabolites are recovered in urine, with the majority being trichloroethanol. Most of the metabolic flux is to trichloroethanol rather than trichloroacetic acid (Kawai et al. 1991). Other minor metabolites, including carbon dioxide and acetylene excreted in the exhaled air, have also been described (Tomicic et al. 2011).

In vivo and *in vitro* evidence from rat experiments suggests that, under conditions of low oxygen supply, 1,1,1-trichloroethane can be reductively dechlorinated, to a limited extent, to free radical intermediates, including 1,1-dichloroethane (Thompson et al. 1985), and eventually to acetylene (Durk et al. 1992). In these experiments, exhaled acetylene accounted for <1% of metabolized 1,1,1-trichloroethane (Thompson et al. 1985). The reductive dechlorination of 1,1,1-trichloroethane appears to be mediated by cytochrome P-450, since putative induction by phenobarbital treatment accelerated the *in vitro* and *in vivo* metabolic formation of acetylene (Durk et al. 1992). The reductive metabolic pathway is not indicated in Figure 3-1 because the study authors indicate that it is a minor metabolic pathway.

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

3.1.4 Excretion

The major route of elimination of absorbed 1,1,1-trichloroethane is exhaled air, regardless of exposure route. After acute-duration inhalation exposure, most 1,1,1-trichloroethane is rapidly excreted unchanged in expired air of humans and animals. Within 1 hour of administration, humans exhaled 44% of the radioactivity that they had inhaled from a single breath of radiolabeled 1,1,1-trichloroethane (Morgan et al. 1970). Humans exposed to 70 or 145 ppm for 4 hours exhaled 60–80% of inhaled 1,1,1-trichloroethane unchanged during a 150-hour period after exposure (Monster et al. 1979). Rapid exhalation of unchanged 1,1,1-trichloroethane was also observed in humans exposed to 35 or 350 ppm for 6 hours, as 71% of the absorbed 1,1,1-trichloroethane was excreted through exhalation after 1.5 hours and >91% of absorbed 1,1,1-trichloroethane was exhaled as the unchanged compound within 9 days of exposure (Nolan et al. 1984). Stewart et al. (1961) performed controlled human exposures to 1,1,1-trichloroethane vapor and identified an exponential decay curve for the concentration of 1,1,1-trichloroethane in expired air. Additional studies demonstrate the predominance of exhalation of unmetabolized 1,1,1-trichloroethane in the excretion of inhaled or absorbed 1,1,1-trichloroethane (Abe and Wakui 1984; Gill et al. 1991; Hajimiragha et al. 1986; Imbriani et al. 1988; Kawai et al. 1991; Laparé et al. 1995; Mizunuma et al. 1995; Nolan et al. 1984; Seki et al. 1975; Tay et al. 1995; Tomicic et al. 2011). Measurement of 1,1,1-trichloroethane concentration in expired air is the most reliable indicator of exposure (Laparé et al. 1995; Nolan et al. 1984).

Similar observations were made in studies of rats (Ikeda and Ohtsuji 1972; Schumann et al. 1982; Schumann et al. 1982), mice (Schumann et al. 1982), and anesthetized dogs (Hobara et al. 1982). Nolan et al. (1984) described the temporal elimination pattern for 1,1,1-trichloroethane in blood and expired air of humans as "triexponential" and estimated half-lives of 44 minutes, 5.7 hours, and 53 hours for the initial, intermediate, and terminal phases, respectively. Raymer et al. (1991) used a two-compartment model to fit experimental observations of the temporal decrease in 1,1,1-trichloroethane concentrations in human breath samples collected for 4 hours after exposure to contaminated atmospheres; elimination half-lives ranged from 0.00 to 0.17 hours for the first compartment and from 1.80 to 6.08 hours for the second compartment.

Exhalation of CO_2 and urinary excretion of metabolites (trichloroethanol and trichloroacetic acid) represent minor elimination pathways for inhaled 1,1,1-trichloroethane (Mitoma et al. 1985). Metabolites in urine, trichloroethanol and trichloroacetic acid, collected for 70 hours postexposure represented approximately 2 and 0.5%, respectively, of the 1,1,1-trichloroethane initially absorbed (Caperos et al. 1982). Nevertheless, observed correlations between urinary concentrations of 1,1,1-trichloroethane metabolites and exposure concentrations indicate that urine analysis may be a useful method of exposure assessment (Caperos et al. 1982; Ghittori et al. 1987; Imbriani et al. 1988; Kawai et al. 1991; Mizunuma et al. 1995; Seki et al. 1975). After 2 hours of inhalation exposure to 175 ppm 1,1,1-trichloroethane, trichloroethanol was excreted rapidly through human urine, with a recovery of 75% of the total amount of trichloroethanol excreted within 24 hours (Johns et al. 2006). PBPK modeling suggests that urinary excretion of trichloroethanol represents 41% of the total metabolites excreted, while trichloroacetic acid excreted in urine represents 10–20% of the total metabolites (Laparé et al. 1995). The urinary excretion of trichloroethanol and trichloroacetic acid decreased linearly over the 70 hours following exposure once peak concentrations were reached in 3 and 40 hours, respectively (Johns et al. 2006). Estimated half-lives for the elimination of trichloroethanol and trichloroacetic acid from human blood after inhalation exposures to 1,1,1-trichloroethane were 10–27 and 70– 85 hours, respectively (Monster et al. 1979; Nolan et al. 1984). The long half-life of trichloroacetic acid is due to binding of this metabolite to plasma proteins. Daily occupational exposure to 1,1,1-trichloroethane progressively increased urinary metabolite levels during the workweek, while levels decreased over the weekend (Seki et al. 1975). This observation is consistent with observations of the rapid clearance of 1,1,1-trichloroethane and its metabolites from animal tissues after inhalation exposure (Dallas et al. 1989; Holmberg et al. 1977; Schumann et al. 1982; Takahara 1986b). The slope of the concentration-time course of 1,1,1-trichloroethane in the chamber air of a closed system in steady state appeared to be constant with respect to amount of chemical injected into

rats, with exposure concentrations ranging from 0.6 to 146 µmol 1,1,1-trichloroethane (Yoshida et al. 1998). This suggests that 1,1,1-trichloroethane was excreted through exhalation proportionally to the amount that was administered to the rats.

Controlled human exposures to approximately 103 ppm 1,1,1-trichloroethane in a 12-m^3 air-conditioned exposure chamber for 6 hours exhibited differences in urinary excretion of trichloroethanol and trichloroacetic acid between men and women, and also differences between women taking hormonal contraceptives and those who were not (Tomicic et al. 2011). However, no differences were observed in the amount of exhaled unchanged 1,1,1-trichloroethane between sexes (Tomicic et al. 2011). Urinary excretion of trichloroethanol throughout the 24 hours after exposure to 1,1,1-trichloroethane was highest in women taking hormonal contraceptive, followed by women not taking hormonal contraceptives, and was lowest in men (Tomicic et al. 2011).

Humans also eliminate ingested 1,1,1-trichloroethane in their exhaled breath (Stewart and Andrews 1966). The pattern of elimination is expected to be similar to that of inhaled 1,1,1-trichloroethane (i.e., exhalation of unchanged 1,1,1-trichloroethane should be the predominant route of excretion; exhalation of CO_2 and urinary excretion of other metabolites are minor routes). This pattern has been observed in animals after inhalation and oral exposure (Mitoma et al. 1985; Reitz et al. 1988; RTI 1987). In rats and mice dosed by gavage with 1,1,1-trichloroethane in vegetable oil 5 days/week for 4 weeks, followed by a single dose of 14C-labeled compound, 85.1 and 92.3% of the doses (3,000 and 4,000 mg/kg in rats and mice, respectively) were recovered as unchanged compound in expired air; respective recovery percentages of metabolite fractions (48 hours after administration) in rats and mice were 0.9 and 2.0% as CO_2, 2.1 and 3.4% as metabolites in urine, and 1.2 and 0.7% as presumed metabolites remaining in the carcasses (Mitoma et al. 1985). In rats exposed to 1,1,1-trichloroethane in drinking water for 8 hours (total dose of 116 mg/kg), the primary route of excretion was rapid elimination of unchanged 1,1,1-trichloroethane in expired air, accounting for >90% of administered doses; only 3% of the ingested dose was metabolized (Reitz et al. 1988). Essentially all ingested 1,1,1-trichloroethane was excreted within 30 hours. Similar results were obtained in gavage studies with rats and mice (RTI 1987). Approximately 14.8% of the chemical in venous blood was eliminated during its first pass through the liver and lungs, respectively, after oral administration of 10 mg 1,1,1-trichloroethane/kg in rats (Mortuza et al. 2018). Excretion via the mother's milk does not appear to be significant for 1,1,1-trichloroethane. Approximately 0.04% of an orally administered dose of 1,1,1-trichloroethane was excreted in the 24-hour milk of lactating goats (Hamada and Tanaka 1995).

The pattern of excretion in humans after dermal exposure is expected to be similar to that of inhaled 1,1,1-trichloroethane: rapid exhalation of 1,1,1-trichloroethane in expired air is the major excretion route and exhalation of CO_2 and urinary excretion of other metabolites are minor routes. Several studies have measured 1,1,1-trichloroethane in the expired breath of humans after (and during) short-term dermal exposure to 1,1,1-trichloroethane (Fukabori et al. 1977; Riihimäki and Pfäffli 1978; Stewart and Dodd 1964), but 1,1,1-trichloroethane exhalation as a percentage of absorbed dose was not quantified in these studies. The concentration of 1,1,1-trichloroethane in expired air can be used as an indicator of dermal uptake of 1,1,1-trichloroethane vapors; however, dermal uptake of vapors is negligible compared with inhalation exposure from vapors (Giardino et al. 1999; Riihimäki and Pfäffli 1978).

Results in animals given 1,1,1-trichloroethane injections indicate that excretion patterns in animals are similar regardless of route. In mice given intraperitoneal injections of 1,1,1-trichloroethane, 88% of the dose was excreted unchanged in expired air and 1% was excreted as metabolites in urine (Takahara 1986a). In rats given intraperitoneal injections, 98.7% of the dose was exhaled as unchanged 1,1,1-trichloroethane (Hake et al. 1960). Within 24 hours of intravenous injection of radiolabeled 1,1,1-trichloroethane, exhalation of radioactivity accounted for 91 and 80% of the administered doses in rats and mice, respectively; only trace amounts of radioactivity remained in the tissues after 24 hours (RTI 1987).

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

Models are simplified representations of a system with the intent of reproducing or simulating its structure, function, and behavior. PBPK models are more firmly grounded in principles of biology and biochemistry. They use mathematical descriptions of the processes determining uptake and disposition of chemical substances as a function of their physicochemical, biochemical, and physiological characteristics (Andersen and Krishnan 1994; Clewell 1995; Mumtaz et al. 2012a; Sweeney and Gearhart 2020). PBPK models have been developed for both organic and inorganic pollutants (Ruiz et al. 2011) and are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Mumtaz et al. 2012b; Ruiz et al. 2011; Sweeney and Gearhart 2020; Tan et al. 2020). PBPK models can also be used to more accurately extrapolate from animal to human, high dose to low dose, route to route, and various exposure scenarios and to study pollutant mixtures (El-Masri et al. 2004). Physiologically based pharmacodynamic (PBPD) models use mathematical

descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic endpoints (Clewell 1995).

There have been many PBPK models developed, some of which were subsequently reconstructed and updated, to describe the amount of 1,1,1-trichloroethane and its metabolites that reach target organs and excretion pathways.

PBPK models developed in Caperos et al. (1982) and Nolan et al. (1984) describe the fate of inhaled 1,1,1-trichloroethane in humans, and both simulate the chemical's absorption, elimination, and excretion through expired air, kinetics of formation, and elimination and the urinary excretion of its metabolites. These models estimate first-order rate constants describing metabolic and urinary elimination of 1,1,1-trichloroethane and its metabolites based on the Fernandez et al. (1977) model for trichloroethylene. Both the Caperos et al. (1982) and the Nolan et al. (1984) models combine the liver compartment, which is a target organ of 1,1,1-trichloroethane metabolism, into the well perfused tissue compartment. The Caperos et al. (1982) model calculates metabolic clearance of 1,1,1-trichloroethane indirectly from data (Humbert and Fernandez 1977) on exposure to trichloroethylene. The Nolan et al. (1984) model describes 1,1,1-trichloroethane concentrations in the expired air and venous blood based on the partition coefficients and metabolism rate constant, which were estimated from data in volunteers who inhaled 35 or 350 ppm of the compound for 6 hours in this study.

Gargas et al. (1986) developed a model based on a four-compartment model that was originally developed for styrene by Ramsey and Andersen (1984), using data obtained from closed-chamber gas uptake studies in rats exposed to 0.2, 1.0, 10, or 210 ppm 1,1,1-trichloroethane. The model describes a chemical exchange compartment (lung), in addition to four other compartments (liver, viscera, muscle/skin, and fat). The model assumes equilibrium between the concentrations in blood leaving the lung and in alveolar air, which is controlled by an experimentally measured blood:air partition coefficient, and the flow-limited tissue uptake of 1,1,1-trichloroethane, by using the experimentally estimated tissue:air partition coefficient. According to the model, 1,1,1-trichloroethane is eliminated through exhalation and exhibits first-order metabolism at a rate constant of 7.8 per hour in the liver.

Reitz et al. (1988) developed a unified PBPK model for 1,1,1-trichloroethane in rats, mice, and humans (based on the previously mentioned styrene model by Ramsey and Andersen [1984]). The model consists of four compartments, including liver, rapidly perfused tissue, slowly perfused tissue, and fat. Tissue volumes and blood and airflow rates employed in the model are listed in Table 3-1. Blood:air and

tissue:air partition coefficients for rats, and blood:air partition coefficients for humans and mice were obtained from Gargas et al. (1986, 1989). Tissue:blood partition coefficients for rats, humans, and mice were calculated by dividing tissue:air partition coefficients for rats, humans, and mice by rat blood:air partition coefficients. Metabolic parameters for the rat (V_{max}, K_m) were derived from rat inhalation exposure data to 150 or 1,500 ppm for 6 hours in Schumann et al. (1982). Uptake of 1,1,1-trichloroethane via bolus gavage was simulated to have a first-order rate constant of 1.25/hour (Reitz et al. 1988).

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

	Human	Rat	Mouse
Weights			
Body weight (kg)	83	0.215	0.029
Liver (%)	3.1	4	4
Rapidly perfused (%)	3.7	5	5
Slowly perfused (%)	61.1	75	78
Fat (%)	23.1	7	4
Flows (L/hour)			
Alveolar ventilation	348	5.11	1.26
Cardiac output	348	5.11	1.26
Liver (% cardiac output)	24	24	24
Rapidly perfused (% cardiac output)	49	53	56
Slowly perfused (% cardiac output)	18	18	18
Fat (% cardiac output)	9	5	2
Partition coefficients			
Blood/air[a]	2.53	5.76	10.8
Liver/air[b]	8.6	8.6	8.6
Rapidly perfused/air[b]	8.6	8.6	8.6
Slowly perfused/air[b]	3.15	3.15	3.15
Fat/air[b]	263	263	263
Biochemical constants[c]			
$V_{max}C$	0.419	0.419	0.419
K_m (mg/L)	5.75	5.75	5.75
K_a ($hour^{-1}$) (first-order rate constant for gastrointestinal absorption	–	1.25	–

[a]Gargas et al. (1989).
[b]Fiserova-Bergerova and Diaz (1986).
[c]$V_{max}C$ and K_m were obtained for the rat from the blood level data of Schumann et al. (1982) by computer optimization. $V_{max}C$ is an allometric measure of maximum velocity of metabolism showing the following relationship with maximum enzyme rate: $V_{max} = V_{max}C \times (\text{body weight}) + 0.7$.

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

Adaptations of the Reitz et al. (1988) model were presented by others (Bogen and Hall 1989; Dallas et al. 1989; DeJongh et al. 1998; Dobrev et al. 2001, 2002; Leung 1992; Poet et al. 2000; Tardif and Charest-Tardif 1999; Yoshida 1993). The predictions of the Dallas et al. (1989), Leung (1992), Yoshida (1993), and DeJongh et al. (1998) models were not validated with experimental data. The Tardif and Charest-Tardif (1999) model simulated blood concentrations in human volunteers during a 4-hour exposure to 400 ppm 1,1,1-trichloroethane.

Bogen and Hall (1989) adapted the Reitz et al. (1988) rat model to gerbils and humans using a scaling factor and added a skin compartment to account for dermal uptake of 1,1,1-trichloroethane for a reference human weighing 70-kg, assuming skin accounted for 6% of the reference body weight.

Dallas et al. (1989) also adapted the Reitz et al. (1988) model to describe the disposition of 1,1,1-trichloroethane in rats following inhalation exposure with the addition of a lung compartment, assuming that the lung:blood partition coefficient was the same as the liver:blood partition coefficient.

Droz et al. (1989a, 1989b) developed a population physiological model for organic solvents, including 1,1,1-trichloroethane (methyl chloroform), based on the Fernandez et al. (1977) PBPK model for trichloroethylene. The chemical-specific distribution parameter values were either obtained directly from an experiment by Droz and Fernandez (1977), as was the case for the blood:gas partition coefficient, or were subsequently derived from the results of this experiment. Pharmacokinetic parameters describing intrinsic metabolic clearance of the chemical were taken from Droz and Fernandez (1977). The metabolite formation and other information about further biotransformation, distribution, and elimination, including metabolic clearance, volumes of distribution, fraction metabolized, and renal clearances, were calculated from Fernandez et al. (1975) and Humbert and Fernandez (1977). The model was used to simulate variability in biological monitoring of solvent exposure of workers at the threshold limit value (TLV) for 8 hours/day, 5 days/week, for 4 and 5 weeks.

Leung (1992) and Yoshida (1993) also adapted the Reitz et al. (1988) model and obtained chemical distributional parameters from the Gargas et al. (1986) model. Michaelis-Menten metabolism, V_{max}, and K_m were scaled allometrically from values in rats (Reitz et al. 1988) for use in the human liver. The Leung (1992) model simulated 1,1,1-trichloroethane concentrations in expired air and blood, as well as concentrations of metabolites of 1,1,1-trichloroethane in urine after human exposure to 350 ppm (occupational exposure limit) for 8 hours/day and 5 days/week, as this represents a typical work schedule. The changes in ventilation and blood flow rates due to exercise were incorporated into the model. The Yoshida (1993) model estimated the steady-state tissue concentrations of 1,1,1-trichloroethane in the Japanese population after daily exposure through inhalation of ambient air and ingestion of drinking water, milk, meat, fish, and vegetation.

Laparé et al. (1995) developed a model to describe 1,1,1-trichloroethane pharmacokinetics in humans after industrial exposure based on data from volunteers exposed to 84.2–175 ppm in a chamber under various scenarios, including rest and workload conditions. The model was built upon previous models with the addition of a gastrointestinal compartment. Tissue:air partition coefficients for lungs, liver, gastrointestinal tract, fat, muscle and skin, and rapidly and slowly perfused tissues were adopted from Fiserova-Bergerova and Diaz (1986). The blood:air partition coefficient was derived empirically through model optimization. The metabolic rate constants of 1,1,1-trichloroethane in the liver with saturable kinetics were derived from Reitz et al. (1988) and the elimination rate constants of metabolites, trichloroethanol and trichloroacetic acid, through metabolism and urinary excretion were obtained by optimizing the model from starting values of Fernandez et al. (1977). The Laparé et al. (1995) model was used to simulate 1,1,1-trichloroethane concentrations in expired air and venous blood, as well as concentrations of urinary metabolites, and was compared with empirical data from Nolan et al. (1984). The model simulations agreed well with experimental data. Modeling results suggested that toxicokinetics of 1,1,1-trichloroethane and its metabolites are increased proportionally with increased exposure duration.

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

Poet et al. (2000) built upon the Reitz et al. (1988) PBPK model by incorporating a skin compartment to determine the dermal permeability of 1,1,1-trichloroethane in rats and humans, and by incorporating Fick's law, which says that dermal permeability is a function of the permeability constant (K_p, cm/hour),

the area exposed (cm^2), and the concentration gradient across the skin (mg/cm^3). The model was used to estimate the skin permeability coefficient (K_{ps}) for dermal absorption of 1,1,1-trichloroethane in rats from water and soil and in humans from water. K_{ps} in rats from non-occluded soil was predicted to be lower than from water.

The Dobrev et al. (2001, 2002) model, which was adapted from Reitz et al. (1988), evaluated interactions for mixed exposures to trichloroethylene, tetrachloroethylene, and 1,1,1-trichloroethane in humans and rats by incorporating terms for various types of competitive metabolism in the liver.

The use of PBPK modeling was explored to establish biological exposure indices. These indices represent the concentration of the chemical or metabolite collected from a worker who has been exposed to an airborne concentration at the American Conference of Governmental Industrial Hygienists (ACGIH) TLV, and for deriving toxicity reference values. The Reitz et al. (1988) model and previously reported values of biochemical parameters were applied in several more studies for such purposes (Leung 1992; Lu et al. 2008; Thomas et al. 1996).

Thomas et al. (1996) paired the Leung (1992) PBPK model with a Monte Carlo simulation to estimate the interindividual variability in the concentrations of 1,1,1-trichloroethane in exhaled breath and urine following industrial exposure, and to compare these results with existing biological exposure indices. The model predictions were further applied to derive the percentage of the occupationally exposed population that were protected based on the current ACGIH threshold limit value. The model estimates suggested that workers were not being adequately protected with the current biological exposure index for end-exhaled air (<10% of the workers were protected); for urinary trichloroacetic acid, half of the workers were protected (Thomas et al. 1996).

Chen et al. (2004) applied a simplified one-compartment model, which handled the entire body as a single compartment by assuming the equilibrium state of the internal chemical concentrations, to estimate interindividual variability in biological exposure indices corresponding to the percentages of protection for workers exposed to TLVs of 1,1,1-trichloroethane.

EPA (2006) explored all available PBPK models published in the literature for 1,1,1-trichloroethane at the time of the report and provided a detailed description of the reconstruction of the models. Based on a thorough evaluation of the model, the Reitz et al. (1988) model was selected for further application in the estimation of internal doses for both humans and rats under a variety of exposure scenarios and

extrapolations across exposure duration, species, and exposure route to support health assessments of 1,1,1-trichloroethane.

Lu et al. (2008) replicated the Gargas et al. (1986) and Reitz et al. (1988) models from the original code and evaluated the two models by comparing their predictions with experimental data in rats and humans. The Reitz et al. (1988) model was selected as the most suitable PBPK model for supporting reference value derivation and further applied in this study for estimation of various internal dose metrics of 1,1,1-trichloroethane and for extrapolations across durations, species, and routes. The model predicted internal dose metrics, including a venous blood concentration of 1.33 mg/L and an area-under-the-curve (AUC) of venous blood concentration of 1.09 mg/L-hour at the end of inhalation exposure to 175 ppm 1,1,1-trichloroethane for 1 hour in humans. The model also back-calculated the external concentrations of continuous exposure at 4, 8, and 24 hours of exposure. The results suggested that blood concentration is a reliable dose metric in duration extrapolation for short term continuous exposure scenarios. Human equivalent concentrations calculated based on average daily AUCs in venous blood were 2-fold higher than those based on average daily AUC concentrations in liver. The study also suggested the potential use of interspecies extrapolation in pharmacokinetics to replace the default pharmacokinetic uncertainty factors in the derivation of the subchronic and chronic inhalation reference concentrations (RfCs).

Valcke and Krishnan (2011a) developed a PBPK model for four volatile organic compounds (VOCs), including benzene, styrene, 1,1,1-trichloroethane, and 1,4-dioxane, based on the Haddad et al. (1996) model in rats, which is a PBPK model solved by a methodology without the use of simulation software. The Valcke and Krishnan (2011a) model assessed the impact of exposure duration and magnitude on the human kinetic adjustment factor, which is a data-derived, chemical-specific adjustment factor for interindividual variability in toxicokinetics, for adults as well as several sensitive subpopulations including neonates (0–30 days), toddlers (1–3 years), and pregnant women. These sensitive subpopulations were assessed to further investigate human interindividual variability in the toxicokinetics of the chemical. The model, which was originally comprised of five compartments in Haddad et al. (1996), including gas exchange, liver, fat, highly perfused, and rest of the body when applied to the general population, was complemented with the compartments of placenta and fetus for pregnant women and neonates. Chemical-specific parameters for 1,1,1-trichloroethane were adapted from Lu et al. (2008) (which was adapted from Reitz et al. 1988), except for the placenta:blood partition coefficients, which were calculated using placenta composition data from Klingler et al. (2003) and Poulin and Krishnan (1995). Physiological parameters originally taken from Haddad et al. (2006) were slightly modified by the study authors' previous work (Valcke and Krishnan 2011b) to allow for the calculation of

physiological parameters as a function of four determinants: body weight, height, age, and sex. The model includes variability terms as multipliers of the calculated physiological parameters for a given set of body weight and height data (Valcke and Krishnan 2011a). The model predicted target dose metrics such as maximum blood concentration and amount metabolized/L liver/24 hours in adults, neonates, toddlers, and pregnant women following various scenarios of inhalation exposure to 1,1,1-trichloroethane. Neonates were predicted to be the most sensitive subpopulation, followed by toddlers, and then general population adults. Valcke and Krishnan (2011a) ultimately found that the human kinetic adjustment factor of up to 2.1 that was derived from the predicted amount of metabolized 1,1,1-trichloroethane was within the default uncertainty factor, and was 2-fold higher than the human kinetic adjustment factor derived from variability in the maximum concentration.

Nong and Krishnan (2007) reconstructed algorithms into steady-state conditions associated with inhalation exposures to 1,1,1-trichloroethane from PBPK models (Leung 1992; Thomas et al. 1996) to estimate an interindividual variability factor of pharmacokinetics to allow for the computation of upper and lower bounds of a probability distribution. The values and probability distributions of input parameters of the PBPK models, including alveolar ventilation, hepatic blood flow, and blood:air partition coefficient, were obtained from Price et al. (2003) and Thomas et al. (1996). Intrinsic clearance of metabolism was calculated as a ratio of maximal metabolic velocity (V_{max}) and Michaelis constant (K_m) (Rane et al. 1977). The interindividual variability factor in pharmacokinetics for 1,1,1-trichloroethane based on the probability-bounds of arterial blood concentration and the rate of metabolism were 1.18 and 1.24, respectively, using probability distribution-defined inputs.

Boogaard et al. (2011) illustrated the derivation of biomonitoring equivalent values corresponding to risk assessment-based derived no-effect levels, using an approach of applying steady-state solutions to a generic physiologically based toxicokinetic (PBTK) model for VOCs developed by Chiu and White (2006) that requires only three chemical-specific parameters: V_{max}, K_m, and the blood:air partition coefficient. The study authors estimated a steady-state blood concentration of 317 µg/L 1,1,1-trichloroethane in humans associated with chronic-duration inhalation exposure to air concentrations of 75 mg/m^3 using chemical-specific parameters for 1,1,1-trichloroethane. The adjusted biomonitoring equivalent corresponding to a risk assessment-based derived no-effect level was estimated at 100 µg/L for the general population (Boogaard et al. 2011).

3.1.6 Animal-to-Human Extrapolations

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

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

Populations at greater exposure risk to unusually high exposure levels to 1,1,1-trichloroethane are discussed in Section 5.7, Populations with Potentially High Exposures.

No information was located regarding potential age-related differences in susceptibility to 1,1,1-trichloroethane in humans. Delays in developmental milestones (pinnae detachment, incisor eruption, and eye opening) and impaired performance in neurobehavior tests were noted in mouse pups of dams exposed to 1,1,1-trichloroethane during later stages of gestation at levels that did not result in apparent maternal

toxicity (Jones et al. 1996). These results suggest that developing organisms may be more susceptible than adults to the toxic effects of 1,1,1-trichloroethane.

Differences in the urinary excretion of trichloroethanol and trichloroacetic acid in humans were observed based on sex and sexual hormone levels after controlled human exposures to inhalation of 103 ppm 1,1,1-trichloroethane for 6 hours (Tomicic et al. 2011). The excretion of trichloroethanol in urine was quantified in men and women was 5.42±2.19 mg/g creatinine and 3.77±1.24 mg/g creatinine, respectively.

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

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

Because 1,1,1-trichloroethane is associated with some cardiovascular effects (see Section 2.5), persons with compromised heart conditions may be at additional risk around high exposure levels of 1,1,1-trichloroethane and should be restricted to some lower level of exposure.

Although no data are available that address this issue, it is possible that individuals with impaired respiratory function (e.g., emphysema, poor perfusion) might excrete less 1,1,1-trichloroethane in a given period than other people, since most of a single dose is expired (Monster et al. 1979; Nolan et al. 1984). In situations of prolonged exposure, such as living near a hazardous waste site, this might contribute to accumulation of 1,1,1-trichloroethane in the body. People with respiratory disease might, therefore, constitute a more susceptible population.

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as biomarkers of exposure, biomarkers of effect, and biomarkers of susceptibility (NAS/NRC 2006).

The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see http://www.cdc.gov/exposurereport/). If available, biomonitoring data for 1,1,1-trichloroethane from this report are discussed in Section 5.6, General Population Exposure.

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 2006). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to 1,1,1-trichloroethane are discussed in Section 3.3.1.

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 2006). 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 effect caused by 1,1,1-trichloroethane are discussed in Section 3.3.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1 Biomarkers of Exposure

Environmental levels of 1,1,1-trichloroethane have been correlated with levels in expired air, blood, and urine.

A significant correlation was observed between ambient concentrations of 1,1,1-trichloroethane and levels of the chemical in expired air of the general population living in various U.S. locations during various seasons (Hartwell et al. 1987; Wallace et al. 1982, 1984, 1985, 1987a, 1987b, 1987c). Levels of 1,1,1-trichloroethane have been quantified in the blood, expired air, and urine of workers exposed to 50 ppm 1,1,1-trichloroethane for 1 week (Monster 1986). Immediately following exposure, urine levels of trichloroethane were 4.9 mg/g creatinine. At 5–15 minutes after exposure, 1,1,1-trichloroethane levels in the blood and expired air were 0.9 mg/L and 210 mg/m^3, respectively. For comparison, the baseline level of 1,1,1-trichloroethane in the blood of people with no characterized exposure sources was 0.0002 mg/L (range <0.0001–0.0034 mg/L) (Hajimiragha et al. 1986). This suggests that levels of 1,1,1-trichloroethane in blood, urine, and expired air may be reliable biomarkers of exposure to 1,1,1-trichloroethane. The National Health and Nutrition Examination Survey (NHANES) reported that 1,1,1-trichloroethane levels in the blood in the general population were typically less than the limit of detection, but occasionally were detectable in the low ppb range (0.0071–2.89 µg/L) in 2011–2018 (CDC 2022).

Levels of metabolites of 1,1,1-trichloroethane, trichloroethanol, and trichloroacetic acid, have also been quantified in the blood, expired air, and urine. Immediately following exposure, urine levels of 1,1,1-trichloroethane and trichloroacetic acid in workers exposed to 50 ppm 1,1,1-trichloroethane for 1 week were 4.9 and 2.5 mg/g creatinine, respectively (Monster 1986). At 5–15 minutes after exposure, blood levels of trichloroethanol and trichloroacetic acid were 0.16 and 2.3 mg/L, respectively (Monster 1986). For comparison, the baseline blood level of trichloroacetic acid has been measured at 0.0214 mg/L (Hajimiragha et al. 1986). Creatinine adjusted urinary trichloroacetic acid was significantly correlated with blood 1,1,1-trichloroethane in a reference population from the Third NHANES (1988–

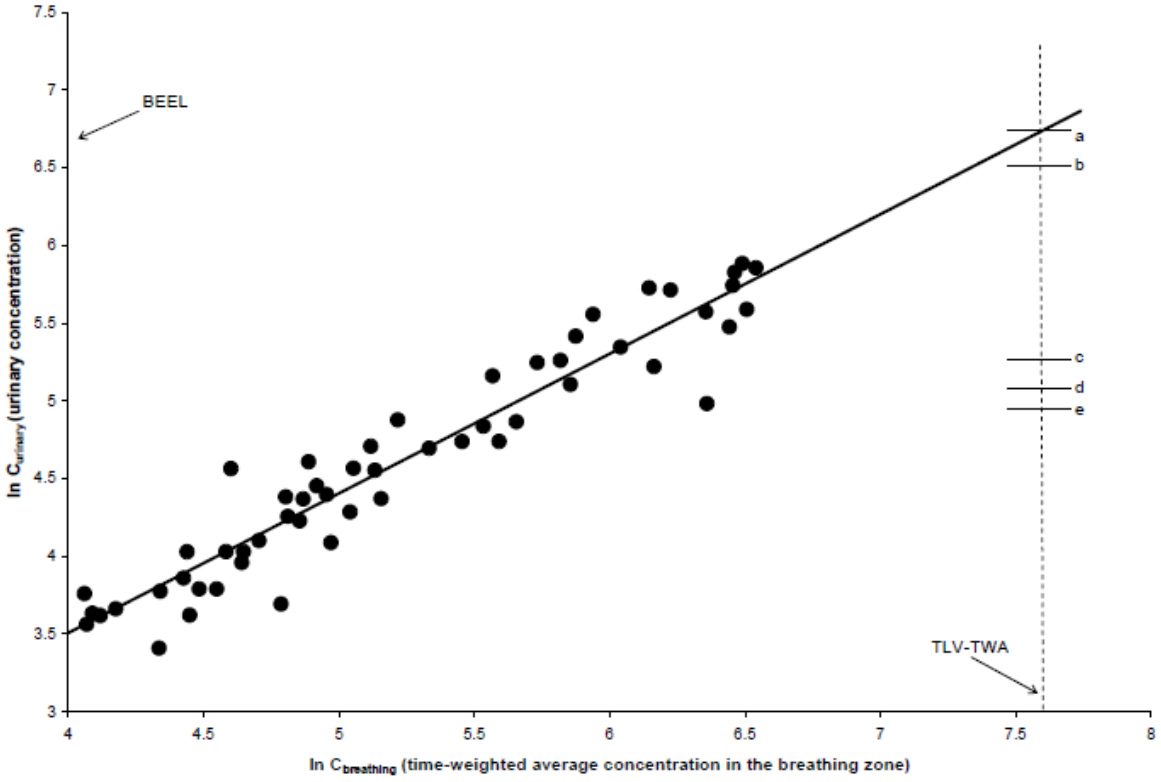
1994) (Calafat et al. 2003). This suggests that levels of the 1,1,1-trichloroethane metabolites of trichloroethanol and trichloroacetic acid in blood and urine may also be effective biomarkers of exposure to 1,1,1-trichloroethane. However, the appearance of trichloroacetic acid in urine is not unique to 1,1,1-trichloroethane, as it has also been identified as a urinary metabolite of trichloroethylene and tetrachloroethylene (Monster 1988). If exposure is known to be solely to 1,1,1-trichloroethane, trichloroacetic acid levels in the urine may be a useful biomarker of exposure because of the relatively long half-life of trichloroacetic acid.

Studies of 1,1,1-trichloroethane levels in expired air or its metabolites in the urine have established a linear correlation between urinary trichloroethanol concentrations and environmental 1,1,1-trichloroethane levels and with 1,1,1-trichloroethane levels absorbed through the lungs (Ghittori et al. 1987; Imbriani et al. 1988; Mizunuma et al. 1995; Monster 1986; Pezzagno et al. 1986; Seki et al. 1975; Stewart et al. 1961). Data from Imbriani et al. (1988) are presented in Figure 3-2, which show this linear relationship between ambient concentrations of 1,1,1-trichloroethane and urinary concentrations of 1,1,1-trichloroethane.

Monster (1986) proposed that the best method for estimating occupational exposure to 1,1,1-trichloroethane was to determine the levels of 1,1,1-trichloroethane and trichloroacetic acid in blood after work on Fridays. Results of Mizunuma et al. (1995) indicated that urinary levels of 1,1,1-trichloroethane (as parent compound) were more closely correlated to 1,1,1-trichloroethane in the ambient air of a group of 50 solvent workers than the major urinary metabolites, trichloroethanol and trichloroacetic acid. Among four adult volunteers (two males and two females) exposed to several different concentrations of 1,1,1-trichloroethane vapors for various exposure durations, levels of parent compound in alveolar air and blood were more closely correlated with exposure level than urinary levels of parent compound or 1,1,1-trichloroethane metabolites (Laparé et al. 1995).

The length of time between 1,1,1-trichloroethane exposure and the measurement of breath, blood, or urine levels is critical to the accurate evaluation of the magnitude of exposure. Up to 90% of the 1,1,1-trichloroethane absorbed by any route is rapidly excreted unchanged in the expired air (Monster et al. 1979; Morgan et al. 1970, 1972b; Nolan et al. 1984; Stewart et al. 1961, 1969). Most of the remaining 10% is accounted for as the urinary metabolites, trichloroethanol and trichloroacetic acid. Furthermore, 1,1,1-trichloroethane is rapidly eliminated from the body; ≥99% is eliminated within 50 hours (Astrand et al. 1973; Monster et al. 1979; Nolan et al. 1984; Stewart et al. 1961).

Figure 3-2. Scatter Diagram Relating TWA of Environmental Concentration and Urinary Concentration of 1,1,1-Trichloroethane in Exposed Workers



Scatter diagram relating the time-weighted average (TWA) of the environmental concentration (in the breathing zone) ($C_{breathing}$) and the urinary concentration ($C_{urinary}$) of 1,1,1-trichloroethane in the exposed workers (Experiment II). The regression line ($C_{urinary}$=0.45xCbreathing+12.6; r=0.95; N=60) is also drawn. The letters appearing on the dotted line (x-axis on the far right) represent the following: a = $C_{urinary}$ value at $C_{breathing}$=1,900 mg/m^3 (threshold limit value [TLV]-TWA); b = 95% lower confidence limit = biological exposure limit; c = hypothetical value of $C_{urinary}$ in an occupationally exposed subject; d = one-sided upper confidence limit (at 95%) of $C_{urinary}$ one-sided lower confidence limit (at 95%) of $C_{urinary}$; and e = one-sided confidence limit (at 95%) of $C_{urinary}$. Classification system: 1 d<b (or d/b<1) = compliance exposure 2 e>b (or e/b>1) = noncompliance exposure 3 any individual that cannot be classified in 1 or 2 = possible overexposure.

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

Source: Imbriani et al. 1988

3.3.2 Biomarkers of Effect

The central nervous system is apparently the most sensitive tissue to 1,1,1-trichloroethane exposure. Decreased psychomotor performance, altered electroencephalogram recordings, ataxia, and anesthesia have been observed in humans after acute-duration exposure (Mackay et al. 1987; Muttray et al. 2000; NIOSH 1975; Torkelson et al. 1958). Mild hepatic effects and decreased blood pressure have also been

noted (Cohen and Frank 1994; Croquet et al. 2003; Stewart et al. 1961; Texter et al. 1979). Numerous animal studies provide supporting evidence for the sensitivity of the central nervous system to acute- and intermediate-duration exposure to 1,1,1-trichloroethane. Adverse cardiovascular effects and mild hepatic effects have also been observed in animals. Indices of central nervous system, hepatic, and cardiovascular effects are of limited value as biomarkers, since many other lipophilic chemicals (including some likely to be present at the same sites as 1,1,1-trichloroethane) may cause similar effects in these target organs.

No specific biomarkers of effect caused by 1,1,1-trichloroethane were found in the literature.

3.4 INTERACTIONS WITH OTHER CHEMICALS

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

Ethanol, when given orally to mice at doses of 0.125–2.0 g/kg, potentiated both the lethality and behavioral effects (inverted screen test) of inhaled 1,1,1-trichloroethane at concentrations ranging from ~200 to 10,000 ppm (Woolverton and Balster 1981). In another study, a 3-day pretreatment of mice with ethanol enhanced 1,1,1-trichloroethane-induced liver toxicity, as indicated by an assay of liver function (bromosulfophthalein retention in plasma), but not an assay of liver damage (ALT levels) (Klaassen and Plaa 1966). Other studies, using only serum enzyme levels to assay liver damage (ALT or AST), found that ethanol markedly and consistently enhanced the hepatotoxicity of more potent chlorinated compounds such as carbon tetrachloride or trichloroethylene, but had no effect on the hepatotoxicity of 1,1,1-trichloroethane (Cornish and Adefuin 1966; Klaassen and Plaa 1967). Ethanol may potentiate the hepatotoxicity of chlorinated alkanes because of its ability to induce CYP2E1 (Ikatsu and Nakajima 1992). The available data indicate that ethanol can enhance the acute neurobehavioral effects of 1,1,1-trichloroethane, but will not cause 1,1,1-trichloroethane to produce severe liver damage (necrosis) like that caused by other chlorinated alkanes such as carbon tetrachloride or 1,1,2-trichloroethane.

Co-exposure of control or ethanol-treated rats to inhaled concentrations of 10 ppm carbon tetrachloride and 200 ppm 1,1,1-trichloroethane did not produce changes in several indices of liver damage (ALT, AST, and liver malondialdehyde) compared with exposure to 10 ppm carbon tetrachloride alone (Ikatsu and Nakajima 1992). This indicates that 1,1,1-trichloroethane may be protective against hepatotoxic effects of cytotoxic haloalkanes. In contrast, co-exposure of ethanol-treated rats to 10 ppm carbon

tetrachloride and 10–50 ppm chloroform produced liver damage that was greater than the additive effects of exposure to each component alone; this synergistic interaction was not observed in rats fed a diet without ethanol (Ikatsu and Nakajima 1992). The results, however, provide no evidence for a synergistic interaction between carbon tetrachloride and 1,1,1-trichloroethane that would enhance the hepatotoxicity of either compound. In experiments with isolated rat hepatocytes, concomitant exposure to chloroform, but not co-exposure to 1,1,1-trichloroethane, potentiated carbon tetrachloride-induced lipid peroxidation (Kefalas and Stacey 1991).

A review study by Pohl and Scinicariello (2011) concluded that 1,1,1-trichloroethane is not expected to enhance the hepatotoxicity of trichloroethylene via cytochrome P-450 induction as the isozymes involved in the metabolism of both chemicals are similar. Additionally, the mixture of 1,1,1-trichloroethane, 1,1-dichloroethane, trichloroethylene, and tetrachloroethylene are not expected to influence each other's toxicity based on their metabolism. This mixture is the most frequently occurring mixture of four volatile organic chemicals and has been found in several NPL sites. A review of vapor intrusion sites assessed by ATSDR found the sites with the three highest concentrations of 1,1,1-trichloroethane in groundwater also contained elevated concentrations of 1,1-dichloroethane and trichloroethylene (ATSDR 2005a, 2005b, 2006; Burk and Zarus 2013). Although exposure to each of the chemicals individually produces similar health effects, limited evidence on the joint toxicity of the chemicals suggests additive interactions on neurological impairment and liver and kidney effects (ATSDR 2004). Administration of a liquid diet containing 2 g/day ethanol for 3 weeks increased the *in vitro* and *in vivo* metabolism of 1,1,1-trichloroethane in rats at all concentrations of exposure to 50, 100, 500, and 1,000 ppm 1,1,1-trichloroethane via inhalation for 6 hours (Kaneko et al. 1994). The enhanced metabolism of 1,1,1-trichloroethane shown by an increase in the urinary excretion of its metabolites indicates that enzymes induced by ethanol affected the metabolism of 1,1,1-trichloroethane *in vivo* at any exposure level. Tetrachloroethylene inhibited the rate of urinary excretion of a 1,1,1-trichloroethane metabolite in rats exposed via inhalation to a mixture containing 350 ppm 1,1,1-trichloroethane and 100 ppm tetrachloroethylene (Koizumi et al. 1982).

Ketones (organic compounds containing a carbonyl group =C=O bonded to two hydrocarbon groups) and ketogenic substances (i.e., substances metabolized to ketones or that produce ketosis in the body) potentiate the hepatotoxicity of certain chlorinated alkanes including carbon tetrachloride, chloroform, and 1,1,2-trichloroethane (Plaa 1988). Although the mechanism of this potentiation is not fully understood, Plaa (1988) proposed enhanced bioactivation of the toxicant through cytochrome P-450 induction. Studies with mice, however, found that treatment with acetone or isopropanol (which is metabolized to acetone) did not enhance the hepatotoxicity of 1,1,1-trichloroethane, but enhanced the

threshold doses of chloroform, 1,1,2-trichloroethane, and trichloroethylene to elevate ALT (Traiger and Plaa 1974). Single intraperitoneal doses of 1,1,1-trichloroethane (1.0 mL/kg) did not produce liver damage (assayed either as elevation in ALT or in concentrations of liver triglycerides) in control mice or in mice with alloxan-induced diabetes (i.e., that were in a state of ketosis) (Hanasono et al. 1975). Other studies examining the influence of agents that enhance cytochrome P-450 metabolism have provided mixed results. The cytochrome P-450 mixed-function oxidase inducer, phenobarbital, enhanced the hepatotoxicity of 1,1,1-trichloroethane in the rat study by Carlson (1973) but not in that by Cornish et al. (1973). In general, the available data suggest that ketones, ketogenic substances, or cytochrome P-450 inducers will not potentiate 1,1,1-trichloroethane hepatotoxicity.

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

Lal and Shah (1970) found that administration of 1,1,1-trichloroethane reduced the hypnosis effects of hexobarbital in male mice. The study found that a short-term inhalation exposure to 1,1,1-trichloroethane at 2,972 ppm (8–96 hours) reduced hexobarbital sleeping time by 50%. The study authors speculated that this decrease in hexobarbital-induced hypnosis was due to 1,1,1-trichloroethane stimulating the liver to better oxidize the hexobarbital, rather than causing a change in the sensitivity of the central nervous system to the depressant.

Human exposure to concentrations of 400 ppm 1,1,1-trichloroethane and 200 ppm m-xylene following 4 hours of inhalation and pharmacokinetic analysis at steady state using PBPK modeling illustrated that combined exposures to the chemicals did not affect 1,1,1-trichloroethane blood levels, but significantly reduced the formation and excretion of its metabolites, trichloroethanol and trichloroacetic acid (Tardif and Charest-Tardif 1999). Ethanol consumption, which was administered at 0.35 g/kg body weight in moderate drinkers 7 days prior to exposure to 175 ppm 1,1,1-trichloroethane via inhalation for 2 hours on two separate occasions significantly increased the apparent metabolic clearance of the compound by 25.4% on average (Johns et al. 2006).

A PBPK model developed by Dobrev et al. (2001, 2002) evaluated interactions of mixed exposures to trichloroethylene, tetrachloroethylene, and 1,1,1-trichloroethane in humans and rats by incorporating terms for various types of competitive metabolism in the liver. The simulated peak 1,1,1-trichloroethane

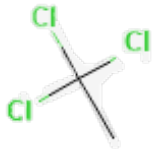
blood level was increased by 42% following co-exposure to 2,000 ppm concentrations of perchloroethylene and 1,1,1-trichloroethane, while the total 1,1,1-trichloroethane metabolites generated were decreased by 84% compared to those after a single exposure to 50 ppm of 1,1,1-trichloroethane only (Dobrev et al. 2002).

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

1,1,1-Trichloroethane is a man-made chlorinated hydrocarbon chemical that was widely used as a solvent and in metal degreasing. It is a synthetic compound. U.S. production of 1,1,1-trichloroethane was to be cut incrementally as per Section 604 of the Clean Air Act and Montreal Protocol, eventually being completely phased out by January 2002, and cease production by 2012 as a result of ozone depletion agreements from the Montreal Protocol (Kapp 2014). While the Montreal Protocol reduced the production of 1,1,1-trichloroethane, some production does continue with a steady decline in the ambient air levels. Information regarding the chemical identity of 1,1,1-trichloroethane is presented in Table 4-1.

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

Characteristic	Information	Reference
Chemical name	1,1,1-Trichloroethane	NLM 2023
Synonym(s) and registered trade name(s)	Methylchloroform; chlorothene; chloroetene; Inhibisol; Aerothene MM; Aerothene TT; Solvent 111; Alpha T	NLM 2022
Chemical formula	$C_2H_3Cl_3$	Haynes et al. 2015
SMILES	CC(Cl)(Cl)Cl	NLM 2023
Chemical structure		NLM 2023
CAS registry number	71-55-6	Haynes et al. 2015

CAS = Chemical Abstracts Service; SMILES = simplified molecular-input line-entry system

4.2 PHYSICAL AND CHEMICAL PROPERTIES

1,1,1-Trichloroethane is a volatile organic compound (VOC). It is slightly soluble in water, and its Henry's law constant suggests that it is readily volatilized from water. Based on the log K_{ow} and log K_{oc} values, 1,1,1-trichloroethane is expected to have high mobility in soil. With a vapor pressure of 124 mm Hg at 25°C, 1,1,1-trichloroethane exists in the atmosphere in the vapor phase. Information regarding physical and chemical properties of 1,1,1-trichloroethane is presented in Table 4-2.

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

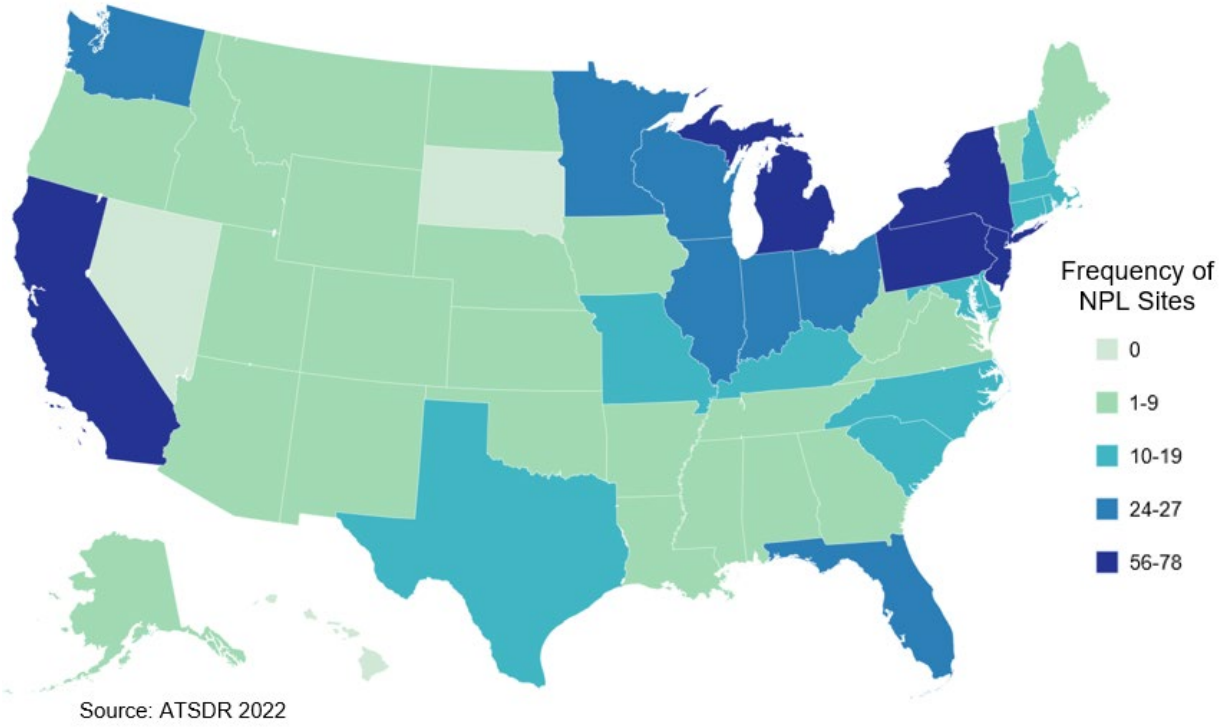
Property	Information	Reference
Molecular weight	133.4	Haynes et al. 2015
Color	Colorless	NIOSH 2019
Physical state	Liquid	Haynes et al. 2015
Melting point	-30°C	Haynes et al. 2015
Boiling point	74°C	Haynes et al. 2015
Density at 20°C/4°C	1.3376	Haynes et al. 2015
Odor	Mild, chloroform-like	NIOSH 2019
Odor threshold: Water Air	 No data 120 ppm 500 ppm	 Amoore and Hautala 1983; Reist and Rex 1977
Taste threshold	No data	
Solubility: Water at 25°C Organic solvent(s)	 1.29 g/L H_2O; slightly soluble in H_2O Soluble in ethanol and chloroform, miscible in diethyl ether; soluble in acetone, benzene, methanol, carbon tetrachloride, and ether	 Haynes et al. 2015; O'Neil 2013
Partition coefficients: Log K_{ow} Log K_{oc}	 2.49 2.03 2.02	 Haynes et al. 2015 Friesel et al. 1984 Chiou et al. 1979
Vapor pressure at 25°C	16.5 kPa (123.8 mmHg)	Haynes et al. 2015
Henry's law constant at 25°C	0.0163 atm-m^3/mole	Warneck 2007
Autoignition temperature	537°C	NLM 2023
Flashpoint	>200°F	NLM 2023
Conversion factors ppm (v/v) to mg/m^3 in air (20°C) mg/m^3 to ppm (v/v) in air (20°C)	 1 ppm = 5.46 mg/m^3 1 mg/m^3 = 0.185 ppm	 NIOSH 2019 Chiou et al. 1980
Explosive limits	7.5–12.5% in air	NIOSH 2019

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

1,1,1-Trichloroethane has been identified in at least 797 of the 1,868 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2022). However, the number of sites in which 1,1,1-trichloroethane has been evaluated is not known. The number of sites in each state is shown in Figure 5-1. Of these sites, 794 are located within the United States, 1 is located in the Virgin Islands, and 2 are located in Puerto Rico (not shown).

Figure 5-1. Number of NPL Sites with 1,1,1-Trichloroethane Contamination



- 1,1,1-Trichloroethane was primarily used in cold-cleaning, vapor degreasing, and ultrasonic cleaning before its use and production decreased due to the Clean Air Act and Montreal Protocol. It continues to be used as a raw material in the manufacture of chlorinated polymers.

- The dominant environmental fate process for 1,1,1-trichloroethane is volatilization to the atmosphere. In the atmosphere, 1,1,1-trichloroethane degrades via interaction with photochemically-produced hydroxyl radicals.

- Since the manufacture and use of 1,1,1-trichloroethane has been phased down, the exposure of most of the general population is expected to be low, but exposure to workers involved in its

manufacture and use could occur. Any exposure that occurs is expected to primarily be through inhalation of contaminated air or ingestion of contaminated water.

1,1,1-Trichloroethane is a synthetic compound that continues to be released to the environment by human industrial activity. It is released to the environment by process and fugitive emissions during its manufacture, formulation, and use in industrial products. Because 1,1,1-trichloroethane is volatile and was used as a solvent in many products, it is most frequently found in the atmosphere due to volatilization during production and use. 1,1,1-Trichloroethane is an ozone depleting substance and has been listed as a class I substance under Section 602 of the Clean Air Act. Class I substances have an ozone depletion potential (ODP) of ≥0.2 and include chlorofluorocarbons (CFCs), halons, carbon tetrachloride, 1,1,1-trichloroethane, and methyl bromide. Although recent estimates have yielded an ODP of 0.12 for 1,1,1-trichloroethane, it is still listed as a class I substance. Under Section 604 of the Clean Air Act as amended in 1990, all production and use of 1,1,1-trichloroethane was scheduled to cease as of January 1, 2002. However, 1,1,1-trichloroethane could still be used for essential applications such as medical devices and aviation safety (for the testing of metal fatigue and corrosion of existing airplane engines and other parts susceptible to corrosion) until January 1, 2005. While the Montreal Protocol reduced the production of 1,1,1-trichloroethane, with a steady decline in the ambient air levels, some production does continue. 1,1,1-Trichloroethane (and other class I substances) could also be produced domestically for export to developing countries as specified in Section 604(e) of the Clean Air Act. This exception to the phase-out ended in 2012 for 1,1,1-trichloroethane (Kapp 2014).

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

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

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

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

The current likelihood of exposure of the general population to 1,1,1-trichloroethane is low. Possible routes of exposure to 1,1,1-trichloroethane are inhalation, dermal contact, or through the ingestion of either contaminated water or food. Exposure by inhalation is expected to predominate. Occupational exposure to 1,1,1-trichloroethane could occur by inhalation or dermal contact during its manufacture and formulation, during its use as a raw material, and during waste handling. Near hazardous waste sites, inhalation is expected to be the predominant route of exposure; however, ingestion of contaminated water may also occur.

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

According to the 1990 amendments to the Clean Air Act and the Montreal Protocol, U.S. production of 1,1,1-trichloroethane was to be cut incrementally, eventually being completely phased out by January 2002. However, during the period beginning on January 1, 2002 and ending on January 1, 2005,

production of limited amounts of 1,1,1-trichloroethane was authorized by the Administrator for use in essential applications, or for the export to developing countries (EPA 2004). Production of 1,1,1-trichloroethane in the United States was meant to end in 2012 as a result of ozone depletion agreements from the Montreal Protocol (Kapp 2014). While the Montreal Protocol reduced the production of 1,1,1-trichloroethane, production does continue. Some facilities still report quantities of 1,1,1-trichloroethane to EPA databases such as the Toxics Release Inventory (TRI) and Chemical Data Reporting (CDR).

Table 5-1 summarizes information on companies that reported the production, import, or use of 1,1,1-trichloroethane for the TRI in 2021 (TRI21 2023). TRI data should be used with caution since only certain types of industrial facilities are required to report. This is not an exhaustive list.

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

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AR	1	10,000	99,999	2, 3, 9, 12
IN	2	100	99,999	9, 12
KY	2	10,000	9,999,999	1, 3, 6
LA	2	100,000	9,999,999	1, 3, 4, 5, 6, 12, 13, 14
NE	1	10,000	99,999	9, 12
OH	3	1,000	99,999	12
PA	1	1,000	9,999	12
SC	1	1,000	9,999	12
TN	5	0	99	7
TX	5	100	999,999	1, 3, 4, 5, 6, 9, 12, 13, 14
UT	1	10,000	99,999	9, 12

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

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

Source: TRI21 2023 (Data are from 2021)

Although domestic production of 1,1,1-trichloroethane was scheduled to cease in 2012, according to EPA's Chemical Data Reporting (CDR) database, nationally aggregated production volume of 1,1,1-trichloroethane ranged from 100,000,000 to <1,000,000,000 pounds between 2016 and 2019 (CDR

2020). Between 2012 and 2015, nationally aggregated production volumes at Axiall Corporation in Calcasieu, Louisiana ranged from 163,472,194 to 192,114,660 pounds (CDR 2016).

The most common method for industrial preparation of 1,1,1-trichloroethane is the reaction of hydrochloric acid with vinyl chloride (obtained from 1,2-dichloroethane) to obtain 1,1-dichloroethane, followed by either thermal or photochemical chlorination. Other methods include the catalyzed addition of hydrogen chloride to 1,1-dichloroethylene, and the direct chlorination of ethane itself, followed by separation from the other products produced (Mertens 2000). Commercial grades of 1,1,1-trichloroethane usually contain some inhibitor (Mertens 2000).

5.2.2 Import/Export

Data on the production volume of 1,1,1-trichloroethane imported at Eagle US 2 LLC in Calcasieu, Louisiana in 2019 is confidential in CDR (CDR 2020). 1,1,1-Tricholorethane was not imported or exported by Axiall Corporation from 2012 to 2015 or by PPG Industries, Inc. in 2011 (CDR 2012, 2016). Export volumes from 2016 to 2019 were listed as Confidential Business Information (CBI) (CDR 2020). The U.S. International Trade Commission (USITC) shows no imports or exports of 1,1,1-trichloroethane since 2014. In 2014, 321,924 kg of 1,1,1-trichloroethane was exported to developing countries (USITC 2023).

5.2.3 Use

1,1,1-Tricholoroethane was formerly widely used as a replacement for other chemicals in metal degreasing and cleaning applications (Doherty 2000). 1,1,1-Trichloroethane was primarily used in cold-cleaning, vapor degreasing, and ultrasonic cleaning to remove grease, oil, and wax from metal parts (Doherty 2000). In addition, 1,1,1-trichloroethane was used in pesticides, rodenticides, insecticides, drain cleaners, and carpet glue; for cleaning leather and suede garments; and for producing aerosols, adhesives, coatings, fluoropolymers, inks, textiles, and electronics (Doherty 2000).

According to EPA's CDR database, 1,1,1-trichloroethane was used as a reactant for industrial gas manufacturing and for plastics material and resin manufacturing at PPG Industries, Inc. in Calcasieu, Louisiana in 2010 and 2011, at Axiall Corporation in Calcasieu, Louisiana from 2012 to 2015, and at Eagle US 2 LLC in Calcasieu, Louisiana from 2016 to 2019 (CDR 2012, 2016, 2020). The database reported that 45,000 pounds were used onsite at Axiall Corporation (CDR 2016).

5.2.4 Disposal

1,1,1-Trichloroethane has been identified as a hazardous waste by EPA, and disposal of this waste is regulated under the Federal Resource Conservation and Recovery Act (RCRA). Specific information regarding federal regulations on 1,1,1-trichloroethane disposal on land, in municipal solid waste landfills, in incinerators, and during underground injection is available in the Code of Federal Regulations.

Disposal of 1,1,1-trichloroethane can be accomplished through its destruction in a high temperature incinerator equipped with a hydrochloric acid scrubber. The destruction and removal efficiency (DRE) for 1,1,1-trichloroethane in hazardous wastes must attain 99.99% (Carroll et al. 1992). During five tests to evaluate a rotary kiln incineration system under baseline conditions and failure conditions, the DRE for 1,1,1-trichloroethane ranged from 99.84 to 99.99982% (Carroll et al. 1992). Other methods that have shown promise for the destruction of 1,1,1-trichloroethane are homogeneous sonochemical treatment for aqueous wastes (Cheung et al. 1991) and a combination of ozonation and ultraviolet treatment for groundwater (Kusakabe et al. 1991). From a laboratory feasibility study, it was concluded that the *in situ* biodegradation of 1,1,1-trichloroethane in soils by methane-oxidizing bacteria was not a viable bioremediation method (Broholm et al. 1991).

5.3 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2022b). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ ≥10 full-time employees; if their facility's North American Industry Classification System (NAICS) codes is covered under EPCRA Section 313 or is a federal facility; and if their facility manufactures (defined to include importing) or processes any TRI chemical in excess of 25,000 pounds, or otherwise uses any TRI chemical in excess of 10,000 pounds, in a calendar year (EPA 2022b).

Table 5-2 shows the reported amounts of 1,1,1-trichloroethane released from facilities that produce, process, or use 1,1,1-trichloroethane.

Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use 1,1,1-Trichloroethane[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AR	1	1	0	0	0	0	1	0	1
IN	2	780	0	0	0	0	780	0	780
KY	2	4,792	14	0	0	11	4,806	11	4,817
LA	2	34,828	440	0	7	0	35,268	7	35,275
NE	1	72	0	0	21	0	72	21	93
OH	3	27	0	0	7	0	27	7	34
PA	1	500	0	0	0	5	500	5	505
AC	1	18	0	0	0	0	18	0	18
TE	5	50	0	0	0	0	50	0	50
TX	5	49	0	0	19	0	49	19	68
UT	1	0	0	0	0	2	0	2	2
Total	24	41,116	454	0	54	18	41,570	72	41,643

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

RF = reporting facilities; UI = underground injection

Source: TRI21 2023 (Data are from 2021)

5.3.1 Air

Estimated releases of 41,116 pounds (~18.65 metric tons) of 1,1,1-trichloroethane to the atmosphere from 24 domestic manufacturing and processing facilities in 2021, accounted for about 99% of the estimated total environmental releases from facilities required to report to the TRI (TRI21 2023). These releases are summarized in Table 5-2.

EPA's National Emission Inventory (NEI) database contains information regarding sources that emit criteria air pollutants (CAPs) and their precursors, and hazardous air pollutants (HAPs) for the 50 United States, Washington DC, Puerto Rico, and the U.S. Virgin Islands. Emissions are estimated from multiple sources, including state and local environmental agencies; the TRI database; computer models for on- and off-road emissions; and databases related to EPA's Maximum Achievable Control Technology (MACT) programs to reduce emissions of HAPs. 1,1,1-Trichloroethane emissions estimated from the 2017 NEI are summarized in Table 5-3 (EPA 2021a).

Table 5-3. National Emission Inventory (NEI) Total National Emissions for 1,1,1-Trichloroethane Estimated by Sector 2017

Sector	Emissions (pounds)
Solvent, degreasing	18,364,705
Solvent, industrial surface coating and solvent use	1,787,213
Solvent, consumer and commercial solvent use	1,104,593
Solvent, non-industrial surface coating	95,397
Industrial processes, not elsewhere classified	77,598
Waste disposal	57,136
Industrial processes, pulp and paper	43,146
Industrial processes, chemical manufacturing	35,758
Fuel combustion, industrial boilers, internal combustion engines, biomass	17,045
Fuel combustion, industrial boilers, internal combustion engines, other	8,158
Fuel combustion, electric generation, coal	5,266
Fuel combustion, electric generation, biomass	3,542
Industrial processes, storage and transfer	2,351
Industrial processes, petroleum refineries	1,894
Fuel combustion, commercial/institutional, biomass	739
Fuel combustion, industrial boilers, internal combustion engines, coal	610
Fuel combustion, industrial boilers, internal combustion engines, natural gas	484
Solvent, graphic arts	402
Industrial processes, cement manufacturing	267
Fuel combustion, electric generation, other	266
Fuel combustion, industrial boilers, internal combustion engines, oil	174
Fuel combustion, commercial/institutional, other	123
Industrial processes, ferrous metals	112
Fuel combustion, electric generation, oil	47
Industrial processes, non-ferrous metals	26
Fuel combustion, commercial/institutional, coal	24
Fuel combustion, commercial/institutional, oil	19
Dust, construction dust	10
Fuel combustion, commercial/institutional, natural gas	3

Table 5-3. National Emission Inventory (NEI) Total National Emissions for 1,1,1-Trichloroethane Estimated by Sector 2017

Sector	Emissions (pounds)
Industrial processes, oil and gas production	3
Industrial processes, mining	3
Bulk gasoline terminals	2
Gas stations	1
Fuel combustion, electric generation, natural gas	1

Source: EPA 2021a

Since 1,1,1-trichloroethane use has declined and production has decreased in the United States, releases to the air from industrial sources are expected to be lower than historical measurements; there are no natural sources of 1,1,1-trichloroethane, but releases may occur from existing soil and water contamination. While data from three sites in the United States showed that emissions of 1,1,1-trichloroethane declined from 18.5 to 3.0 Gg/year from 1997 to 2002, 1,1,1-trichloroethane was still released to the atmosphere despite decreased production as established by the Montreal Protocol in 1996 (Millet and Goldstein 2004).

The only natural source of 1,1,1-trichloroethane emissions proposed is biomass burning, and global emissions from this source were estimated to be around 2 to 10 Gg/year (Simpson et al. 2007). However, field measurements from five continents collected for >10 years did not show that biomass burning is a significant source of 1,1,1-trichloroethane in the atmosphere, and global emissions from biomass burning are not expected to exceed 0.014 Gg/year (Simpson et al. 2007).

Small amounts of 1,1,1-trichloroethane are also released to the atmosphere from coal-fired power plants (Garcia et al. 1992), incineration of hospital wastes (Green and Wagner 1992; Walker and Cooper 1992), incineration of military nerve agents (Mart and Henke 1992), incineration of industrial wastes containing certain plastics and waste solvents (Nishikawa et al. 1992, 1993), and incineration of municipal wastewater sludge (EPA 1991). 1,1,1-Trichloroethane contained in industrial products is released into the atmosphere during the manufacture and use of these products and during waste handling. 1,1,1-Trichloroethane can enter the atmosphere via the air-stripping treatment of wastewater. Volatilization, which accounts for ≈100% of removal in wastewater, occurs during this process (Kincannon et al. 1983a). Volatilization from waste lagoons is also likely (Shen 1982).

5.3.2 Water

Estimated releases of 454 pounds (~0.21 metric tons) of 1,1,1-trichloroethane to surface water from 24 domestic manufacturing and processing facilities in 2021, accounted for 1% of the estimated total environmental releases from facilities required to report to the TRI (TRI21 2023). This estimate includes releases to wastewater treatment and publicly owned treatment works (POTWs) (TRI21 2023). These releases are summarized in Table 5-2.

1,1,1-Trichloroethane can be released to surface water from the wastewater of industries in any of the industrial classifications that use or produce this compound. Higher concentrations of 1,1,1-trichloroethane have been found in surface waters near known industrial sources, such as effluent outfalls or disposal sites, compared to the levels found upstream from these sources (Hall 1984; Kaiser and Comba 1986; Kaiser et al. 1983; Wakeham et al. 1983).

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

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

5.3.3 Soil

Estimated releases of 54 pounds (~0.02 metric tons) of 1,1,1-trichloroethane to soil from 24 domestic manufacturing and processing facilities in 2021, accounted for about <1% of the estimated total environmental releases from facilities required to report to the TRI (TRI21 2023). These releases are summarized in Table 5-2.

Land application of sewage sludge that may contain minute amounts of 1,1,1-trichloroethane may slightly elevate the level of 1,1,1-trichloroethane in agricultural soil, but the level is not expected to be of environmental concern in the majority of cases (Wilson et al. 1994). The most likely routes for soil contamination are through accidental spills, contamination of soil by landfill leachates, leaching of contaminated surface waters from treatment/storage lagoons, wet deposition, and possibly the percolation of contaminated rainwater through soil.

5.4 ENVIRONMENTAL FATE

5.4.1 Transport and Partitioning

Air. 1,1,1-Trichloroethane has a vapor pressure of 124 mm Hg at 20°C, which means that it exists in the vapor phase in the atmosphere (Haynes et al. 2015). Since this compound has low water solubility, some vapor-phase 1,1,1-trichloroethane will be removed from the air via washout by rain and transported to the terrestrial surface. It has been identified in rainwater (Jung et al. 1992; Kawamura and Kaplan 1983; Plumacher and Renner 1993; Rasmussen et al. 1982). 1,1,1-Trichloroethane removed by rainwater would be expected to re-volatilize rapidly to the atmosphere. Because of its long half-life of 5–6.9 years, tropospheric 1,1,1-trichloroethane will be transported to the stratosphere, where it will participate in the destruction of the ozone layer. It will also undergo long-distance transport from its sources of emissions to other remote and rural sites. This is confirmed by the detection of this synthetic chemical in forest areas of Northern and Southern Europe and in remote sites (Ciccioli et al. 1993).

Water. 1,1,1-Trichloroethane is a VOC with low water solubility (1,290 mg/L at 25°C) (Haynes et al. 2015). The experimental Henry's law constant measured for this compound is 0.0163 atm-m^3/mole at 25°C (Warneck 2007); this suggests that volatilization from water should be the dominant fate process. Volatilization of 1,1,1-trichloroethane from water has readily occurred in the laboratory, in the field, and during wastewater treatment (Dilling 1977; Dilling et al. 1975; Kincannon et al. 1983b; Piwoni et al. 1986; Wakeham et al. 1983). Partitioning of 1,1,1-trichloroethane also has occurred from soil to air and from the groundwater of unconfined aquifers to soil (EPA 1983; Piwoni et al. 1986).

Sediment and Soil. Based on the experimental values for the log octanol/water partition coefficient (K_{ow}), 2.49 (Hansch and Leo 1985), and log K_{oc}, in the range of 2.02–2.03 (Chiou et al. 1979; Friesel et al. 1984), 1,1,1-trichloroethane would be expected to show high mobility in soil and readily leach into

groundwater (Lyman et al. 1990; Swann et al. 1983). In surface waters, 1,1,1-trichloroethane would not be expected to show appreciable adsorption to sediment or suspended organic material.

Other Media. An experimental bioconcentration factor (BCF) of 9 (bluegill sunfish) has been determined for 1,1,1-trichloroethane (Barrows et al. 1980), suggesting that in fish and other aquatic organisms, uptake from water should not be an important fate process.

5.4.2 Transformation and Degradation

Air. The dominant atmospheric fate process for 1,1,1-trichloroethane is predicted to be degradation by interaction with photochemically-produced hydroxyl radicals. Rate constants for this gas-phase reaction range from 0.95×10^{-14} to 1.2×10^{-14} cm^3/mol-second (Finlayson-Pitts et al. 1992; Jiang et al. 1992; Lancar et al. 1993; Talukdar et al. 1992).

1,1,1-Trichloroethane is degraded via H-atom abstraction to $CCl_3 \cdot CH_2$ and reacts with O_2 to yield the peroxy radical ($CCl_3CH_2O_2$) (DeMore 1992; Spence and Hanst 1978). Using an estimated atmospheric hydroxyl ($\cdot OH$) radical concentration of 5.0×10^5 mol/cm^3 (Atkinson 1985), the more recent rate constants translate to a calculated lifetime or residence time of ~6 years. The estimated atmospheric lifetime of 1,1,1-trichloroethane, which incorporates all removal processes, was also estimated to be ~6 years (Prinn et al. 1987, 1992). This indicates that the predominant tropospheric sink of 1,1,1-trichloroethane is through its reaction with hydroxyl radicals.

Photolytic degradation experiments have been performed in the presence of NO and NO_2; 1,1,1-trichloroethane underwent <5% degradation in 24 hours in the presence of NO (Dilling et al. 1976). In a smog chamber experiment in the presence of NOx, 1,1,1-trichloroethane showed a disappearance rate of 0.1% per hour (Dimitriades and Joshi 1977). Other studies have also concluded that 1,1,1-trichloroethane has low potential to form ozone as a result of photochemical reaction in the presence of NOx (Andersson-Skold et al. 1992; Derwent and Jenkin 1991). Under laboratory conditions designed to mimic atmospheric smog conditions, direct photochemical irradiation of 1,1,1-trichloroethane in the presence of elemental chlorine was performed. 1,1,1-Trichloroethane was the least reactive and thus the most stable of all chloroethanes under these conditions (Spence and Hanst 1978).

Direct photochemical degradation of 1,1,1-trichloroethane in the troposphere is not expected to be an important fate process, because there is no chromophore for absorption of ultraviolet light (>290 nm)

found in sunlight at tropospheric altitudes (Hubrich and Stuhl 1980; Vanlaethem-Meuree et al. 1979). A laboratory experiment performed in sealed Pyrex ampules showed loss of 1,1,1-trichloroethane in 2 weeks under the influence of sunlight; however, catalysis by the Pyrex surface was probably responsible for the enhanced reactivity (Buchardt and Manscher 1980).

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

Water. Slow biodegradation of 1,1,1-trichloroethane can occur under both anaerobic and aerobic conditions. Anaerobic degradation of 1,1,1-trichloroethane is thought to occur predominantly through reductive dechlorination by methane-producing bacteria (Vargas and Ahlert 1987; Vogel and McCarty 1987) and by sulfate-reducing organisms (Cobb and Bouwer 1991; Klecka et al. 1990). Determined experimental half-lives for anaerobic degradation using mixed culture bacteria ranged from 1 day to 16 weeks in the laboratory (Bouwer and McCarty 1983b, 1984; Hallen et al. 1986; Parsons et al. 1985; Vogel and McCarty 1987; Wood et al. 1985). *Desulfitobacterium sp.* strain PR reductively dechlorinated 1,1,1-trichloroethane to monochloroethane in 15 days (Ding et al. 2014). Based on a study from an injection well, after 3 months of injection, the predicted half-life of 1,1,1-trichloroethane in an aquifer was 200–300 days (Bouwer and McCarty 1984). Results obtained in a grab sample study of an aquifer suggest that anaerobic biodegradation of 1,1,1-trichloroethane will not occur (Wilson et al. 1983); however, the spiked concentration of 1,1,1-trichloroethane in the study, 1 mg/L, was in a range determined to be toxic to microorganisms (EPA 1979; Benson and Hunter 1976; Vargas and Ahlert 1987). Another grab sample study, performed using more realistic concentrations, indicates that 1,1,1-trichloroethane slowly degrades under anaerobic conditions to 1,1-dichloroethane in groundwater (Parsons and Lage 1985; Parsons et al. 1985). However, when mixed anaerobic cultures were provided with acetate as primary substrate, the biodegradation of secondary substrate 1,1,1-trichloroethane occurred even without acclimation at concentrations exceeding 1 mg/L (Hughes and Parkin 1992). A laboratory study showed that anaerobic biodegradation of 1,1,1-trichloroethane did not occur under denitrification conditions even after 8 weeks of incubation (Bouwer and McCarty 1983a).

Aerobic biodegradation in surface water and groundwater is not likely to be an important fate process since experimental studies did not indicate significant aerobic degradation of 1,1,1-trichloroethane (Klecka et al. 1990; Mudder and Musterman 1982; Wilson and Pogue 1987). One study showed that 1,1,1-trichloroethane underwent aerobic degradation in the presence of Fe^{+2}/porphyrin solution (82% in 21 days), thought to be a catalyzed reductive chlorination (Klecka and Gonsior 1984). It is difficult to interpret these results in terms of the potential for environmental significance. One study reported that 1,1,1-trichloroethane underwent moderate biodegradation with significant concomitant volatilization (Tabak et al. 1981); however, experimental details are not sufficient to rule out loss due solely to volatilization. Halogenated aliphatic hydrocarbons, including 1,1,1-trichloroethane, act as cometabolic substrates for certain aerobic chemotrophs. In such cases, the organisms grow on another substrate and the enzymes induced under the particular growth conditions fortuitously biodegrade the halogenated aliphatics (Leisinger 1992). Such aerobic biodegradation of 1,1,1-trichloroethane up to a concentration of 1.2 mg/L was observed with methane-oxidizing (methanotrophic) bacteria isolated from an aquifer (Arvin 1991). Aerobic biodegradation may occur in the presence of adapted organisms; in aerobic groundwater collected from seven sites contaminated with chlorinated hydrocarbons, degradation was observed in samples from five sites, with lag periods of 0–92 days (Willmann et al. 2023). Degradation typically stagnated after substantial reduction (residual levels of 0.0050–0.34 mg/L remaining), and only one site degraded to a level below the detection limit.

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

Products from the abiotic degradation of 1,1,1-trichloroethane have also been identified. Acetic acid can arise from the hydrolysis of 1,1,1-trichloroethane (calculated half-life of 1.2 years at 25°C and pH 7). Elimination of HCl can produce 1,1-dichloroethene (Hallen et al. 1986; Parsons et al. 1985; Vogel and McCarty 1987). The calculated half-life for this reaction is 4.8 years at 25°C and pH 7 (Ellenrieder and Reinhard 1988). The half-lives of abiotic degradation of 1,1,1-trichloroethane by reaction with nucleophiles, such as HS^- and S_2O^{2-}, which might be present in water, should be insignificant compared to

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

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

Other Media. Uptake of 1,1,1-trichloroethane has been observed in *Eucalyptus camaldulensis* seedlings and wood (Graber et al. 2007). Competition between 1,1,1-trichloroethane and trichloroethene for sorption sites occurred during both seedling uptake and wood sorption, indicating that uptake of compounds is impacted by the number of VOCs present and may be lower than expected when more contaminants are present.

5.5 LEVELS IN THE ENVIRONMENT

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

Table 5-4 shows the limit of detections typically achieved by analytical analysis in environmental media. An overview summary of the range of concentrations detected in environmental media is presented in Table 5-5.

Table 5-4. Lowest Limit of Detection for 1,1,1-Trichloroethane Based on Standards[a]

Media	Detection limit	Reference
Blood	0.010 ng/mL	CDC 2018
Municipal and industrial wastewater	0.030 µg/L	EPA 2021b
Drinking water	0.005 µg/L	EPA 1995
Groundwater	5 µg/L	EPA 1986
Soil and sediment	0.275 µg/kg	EPA 2006b
Air	1 pptv	EPA 2019

[a]Detection limits based on using appropriate preparation and analytics. These limits may not be possible in all situations

Table 5-5. Summary of Environmental Levels of 1,1,1-Trichloroethane

Media	Low	High	For more information
Outdoor air (ppbv)	<0.015	0.48	Section 5.5.1
Indoor air (ppbv)	0.05	150	Section 5.5.1
Surface water (ppb)	ND	0.5	Section 5.5.2
Groundwater (ppb)	<0.05	390	Section 5.5.2
Drinking water (ppb)	0.0002	500	Section 5.5.2
Food (ppb)	–	–	Section 5.5.4
Soil and sediment (ppb)	ND	1,600	Section 5.5.3

ND = not detected

Presented in Table 5-6 is a summary of the range of concentrations detected in environmental media at NPL sites.

Table 5-6. 1,1,1-Trichloroethane Levels in Water, Soil, and Air of National Priorities List (NPL) Sites

Medium	Median[a]	Geometric mean[a]	Geometric standard deviation[a]	Number of quantitative measurements	NPL sites
Water (ppb)	93.5	112	27.7	626	322
Soil (ppb)	1,500	1,830	90.4	219	155
Air (ppbv)	3	5.17	35.2	106	71

[a]Concentrations found in ATSDR site documents from 1981 to 2022 for 1,868 NPL sites (ATSDR 2022). Maximum concentrations were abstracted for types of environmental media for which exposure is likely. Pathways do not necessarily involve exposure or levels of concern.

5.5.1 Air

Table 5-7 shows the mean ambient air 1,1,1-trichloroethane concentrations measured by EPA, state, local, and tribal air pollution control agencies for the Air Quality System (AQS). Mean ambient air concentrations are typically <0.015 ppbv, with a maximum mean concentration of 0.48 ppbv in the last 5 years (EPA 2022a).

Table 5-7. Percentile Distribution of Mean 1,1,1-Trichloroethane Concentrations (ppbv) Measured in Ambient Air at Locations Across the United States

		Percentile				
Year	Number of U.S. locations	25th	50th	75th	95th	Maximum
2017	201	0	0	0.0025	0.0085	0.11
2018	201	0	0	0.0016	0.0145	0.48
2019	151	0	0	0.0008	0.0170	0.16
2020	159	0	0	0.0002	0.0138	0.03
2021	164	0	0	0	0.0061	0.46
2022	120	0	0	0	0.0043	0.05

Source: EPA 2022a (data current as of August 2023)

The East Palestine, Ohio train derailment occurred on February 3, 2023, and involved several train cars containing hazardous materials. 1,1,1-Trichloroethane was below the reporting limits (<0.005–0.064 ppbv) in the majority of 1,190 air samples collected following the derailment to mid-July, 2023 (EPA 2023). An average of 0.027 ppbv 1,1,1-trichloroethane was detected in five samples collected on March 10, 2023.

EPA's compilation of 15 studies of background indoor air concentrations found a 4–100% detection rate for 1,1,1-trichloroethane in 2,658 U.S. resident samples between 1981 and 2004 (EPA 2011). The background medians ranged from 0.3 to 26 µg/m^3, 95th percentiles ranged from 3.4 to 130 µg/m^3, and maximum values ranged from 9.3 to 817 µg/m^3. One possible source of indoor air 1,1,1-trichloroethane is vapor intrusion from polluted soil or groundwater. Four sites included in the EPA Vapor Intrusion Database had reported indoor air concentrations of 0.27–34.00 µg/m^3 (EPA 2012). Indoor air concentrations of 0.03–200 µg/m^3 were detected at 15 vapor intrusion sites included in ATSDR public health assessments between 1994 and 2009. In indoor air of New Jersey suburban and rural homes, the maximum indoor air concentration of 1,1,1-trichloroethane was 9.3 µg/m^3 (Weisel et al. 2008). At the

National Aeronautics and Space Administration Research Park in San Francisco in 2003 and 2004, 513 samples of indoor air, 113 samples of outdoor air, and 68 samples of background outdoor air were analyzed for 1,1,1-trichloroethane and other VOCs (Brenner 2010). In indoor air, 1,1,1-trichloroethane was detected in 99.6% of the samples at a mean concentration of 0.212 µg/m^3 with a standard deviation of 0.258 µg/m^3 and a maximum concentration of 0.248 µg/m^3 (Brenner 2010). 1,1,1-Trichloroethane was detected in all outdoor air samples at a mean concentration of 0.185 µg/m^3, with a standard deviation of 0.073 µg/m^3 and a maximum concentration of 0.856 µg/m^3 (Brenner 2010). In background outdoor air, 1,1,1-trichloroethane was detected in all samples at a mean concentration of 0.182 µg/m^3, with a standard deviation of 0.0382 µg/m^3 and a maximum concentration of 0.307 µg/m^3 (Brenner 2010).

5.5.2 Water

The Water Quality Portal (WQP) database compiles water quality data across the United States from EPA, the U.S. Geological Survey (USGS), and the U.S. Department of Agriculture (USDA). A summary of the data available for surface and groundwater is provided in Table 5-8 (WQP 2023). 1,1,1-Trichloroethane was not commonly detected in either media, although surface water sampling campaigns were more limited, and higher concentrations were reported in groundwater. In 21 samples of groundwater at the National Aeronautics and Space Administration (NASA) Research Park in San Francisco in 2003 and 2004, 1,1,1-trichloroethane was detected in 43% of the samples at a mean concentration of 3.622 µg/L, with a standard deviation of 2.91 µg/L and a maximum concentration of 10 µg/L (Brenner 2010). 1,1,1-Trichloroethane was <0.5 µg/L (the reporting limit) in 221 groundwater samples collected from 28 monitoring wells in Pennsylvania between 2015 and 2019 (USGS 2022). In water from principal aquifers in the United States surveyed between 1991 and 2010, 1,1,1-trichloroethane was detected in 0.88% of shallow groundwater beneath agricultural land (0.68% >0.2 µg/L) and 10.71% of shallow groundwater beneath urban land (3.51% >0.2 µg/L) (USGS 2014a, 2014b).

Table 5-8. Summary of Concentrations of 1,1,1-Trichloroethane (µg/L[a]) Measured in Surface and Groundwater Across the United States[b]

Year	Average	Maximum	Number of samples	Percent detected
Surface water				
2018	–	–	510	0%
2019	–	–	458	0%
2020	–	–	199	0%
2021	0.012	0.012	157	0.64%

Table 5-8. Summary of Concentrations of 1,1,1-Trichloroethane (µg/L[a]) Measured in Surface and Groundwater Across the United States[b]

Year	Average	Maximum	Number of samples	Percent detected
2022	0.5	0.5	43	2.3%
2023[b]	–	–	29	0%
Groundwater				
2018	0.25	0.7	1,303	1.7%
2019	0.21	0.6	2,009	1.8%
2020	0.32	1.4	1,708	2.5%
2021	26	390	2,264	1.7%
2022	43	305	2,962	1.5%
2023[b]	0.29	0.42	667	0.90%

[a]1 µg/L = 1 ppb.
[b]As of August 2, 2023.

Source: WQP 2023

Under the Safe Drinking Water Act, the EPA conducts compliance monitoring data reviews across 6-year periods of drinking water monitoring data submitted by states and primary agencies. Between 2006 and 2011, 1,1,1-trichloroethane was reported in 1.3% of 374,181drinking water samples collected from across all 50 states (EPA 2016). Reported concentrations ranged from 0.0002 to 500 µg/L, with an average of 3.03 µg/L. During a survey of principal aquifers in the United States between 1991 and 2010, 1,1,1-trichloroethane was detected in 4.88% of all sampled areas of aquifers used for drinking water, or up to 19.35% of areas in a single aquifer (USGS 2014a, 2014b). Only 0.57% of the detections in all sample aquifers were >0.2 µg/L.

Due to waste-disposal activities at the Idaho National Laboratory, VOCs, including 1,1,1-trichloroethane, are present in water from the eastern Snake River Plain aquifer in Idaho (USGS 2019). 1,1,1-Trichloroethane was one of the primary VOCs detected in water samples collected from 15 aquifer wells between 2016 and 2018, with concentrations ranging from 0.3 to 0.4 µg/L (USGS 2019). 1,1,1-Trichloroethane was detected in one well at the Radioactive Waste Management Complex at the Idaho National Laboratory at concentrations ranging from 0.411 to 0.735 µg/L from 2016 to 2018 (USGS 2019). The concentration of 1,1,1-trichloroethane was greater than the MCL for drinking water in one well near Test Area North. 1,1,1-Trichloroethane was not detected in groundwater samples (n=82) collected from the Palermo Wellfield Superfund site between 2018 and 2020 (WQP 2023). 1,1,1-Trichloroethane was below

the reporting limits (0.27–100 µg/L) in surface water samples collected in February 2023, after the East Palestine, Ohio train derailment (EPA 2023).

5.5.3 Sediment and Soil

Recent monitoring data on the occurrence of 1,1,1-trichloroethane in soil are lacking. In surface soil samples compiled by WQP in 2006, 1,1,1-trichloroethane was not detected (WQP 2023). In subsurface soil and sediment, the concentration of 1,1,1-trichloroethane ranged from 1.1 to 1,600 µg/kg in samples collected between 2006 and 2011 (WQP 2023). Recent data are limited to bed sediment samples (n=28) collected in 2019 in which 1,1,1-trichloroethane was not detected (WQP 2023). The limited data on the concentration of 1,1,1-trichloroethane in soil may be due to its rapid volatilization from soil, its ability to leach through soil, or both. Sub-slab soil gas detections of 160.00–5,251.64 µg/m^3 were reported across four sites in the EPA Vapor Intrusion Database (EPA 2012).

In two grab soil samples taken in 1980 from two former sludge lagoons of a solvent recovery operation at Southington, Connecticut, the measured concentrations of 1,1,1-trichloroethane were 23,000 and 120,000 ppb (Hall 1984). 1,1,1-Trichloroethane was not detected in five surface soil samples collected more recently at the Palermo Wellfield Superfund site (WQP 2023).

5.5.4 Other Media

Limited data on the occurrence of 1,1,1-trichloroethane in other media were identified. Samples of three different species of fish collected in Honolulu, Hawaii, between 2010 and 2014 did not contain 1,1,1-trichloroethane (WQP 2023). Previously, 1,1,1-trichloroethane has been detected in fish and shrimp taken from the Pacific Ocean at average concentrations of 2.7 and <0.3 ppm, respectively (Young et al. 1983), and in clams and oysters from Lake Pontchartrain, Louisiana, with mean concentrations ranging from 39 to 310 ppm (Ferrario et al. 1985). 1,1,1-Trichloroethane was previously detected in 2 of 265 table-ready foods of the Food and Drug Administration (FDA) Total Diet Study at an average concentration of 12.7 ppb (Heikes et al. 1995). The compound has not been included in the more recent FDA Total Diet Studies from 2003 to 2017.

1,1,1-Trichloroethane has been detected in four shoe and leather glues in Denmark in the concentration range 0.1–2.7% (wt/wt) (Rastogi 1992). Six samples of glues manufactured in the United States and

Europe, which were used for assembling various consumer goods and toys, contained 1,1,1-trichloroethane in the range of 0.002–97.5% (wt/wt) (Rastogi 1993). In various brands of imported typing correction fluids in Singapore, the equilibrium vapor phase concentration of 1,1,1-trichloroethane ranged from <1 to 95% (v/v) (Ong et al. 1993).

5.6 GENERAL POPULATION EXPOSURE

Since the manufacture and use of 1,1,1-trichloroethane has been reduced, the exposure of the general population should be insignificant. However, since there is some evidence of 1,1,1-trichloroethane releases to the water, air, and soil, the general population is potentially exposed to low levels of 1,1,1-trichloroethane through ingestion and inhalation of contaminated water and air, respectively. 1,1,1-Trichloroethane was used as a component of adhesives for food packaging, and this practice may have contributed to human exposure by ingestion (Miller and Uhler 1988). According to NHANES data from 2011 to 2018, the mean blood concentration of 1,1,1-trichloroethane in the total population is below the limit of detection (0.010 ng/mL) (CDC 2022).

ATSDR's three-compartment Shower and Household-Use Exposure (SHOWER) model predicts air concentrations in the shower stall, bathroom, and main house throughout the day by estimating the contribution from showering or bathing and the contribution from other water sources in the house, such as the dishwasher, clothes washer, and faucets. This information along with human activity patterns are used to calculate a daily time-weighted average exposure concentration via inhalation exposure and from dermal uptake from skin contact. ATSDR's SHOWER model is available by sending a request to showermodel@cdc.gov. Using average drinking water concentrations (EPA 2016; see Section 5.5.2) and the reporting level for AQS detections, as 1,1,1-trichloroethane is typically not detected in average outdoor air (EPA 2022a; see Section 5.5.1), Reasonable Maximum Exposure (RME) levels were calculated for different exposure groups and are reported in Table 5-9 (ATSDR 2023).

Table 5-9. RME Daily Inhalation Dose (µg/m^3) and Administered Dermal Dose (µg/kg/day) for the Target Person

Exposure group	Inhalation	Dermal
Birth to < 1 year	2.4	0.023
1–<2 years	2.4	0.021
2–<6 years	2.4	0.018
6–<11 years	2.4	0.015
11–<16 years	2.4	0.012

Table 5-9. RME Daily Inhalation Dose (µg/m^3) and Administered Dermal Dose (µg/kg/day) for the Target Person

16–<21 years	2.4	0.011
Adult	2.4	0.011
Pregnant and breastfeeding women	2.4	0.011

RME = Reasonable Maximum Exposure

Source: ATSDR 2023

Vapor intrusion may also be a potential source of 1,1,1-trichloroethane exposure, as vapor intrusion has been observed for several VOCs with similar properties. EPA's compilation of 15 studies of background indoor air concentrations found a 4–100% detection rate for 1,1,1-trichloroethane in 2,658 U.S. resident samples between 1981 and 2004 (EPA 2011). The background medians ranged from 0.3 to 26 µg/m^3, 95th percentiles ranged from 3.4 to 130 µg/m^3, and maximum values ranged from 9.3 to 817 µg/m^3. EPA's Vapor Intrusion Database reported indoor air concentrations of 0.27–34.00 µg/m^3 and sub-slab soil gas concentrations of 160.00–5,251.64 µg/m^3; attenuation factors ranged from 2.6x10^{-4} to 0.079 (EPA 2012). A long-term study of vapor intrusion at the NASA Ames Research Center in San Francisco detected 1,1,1-trichloroethane in 43% of groundwater samples below the research park at a mean concentration of 3.622 µg/L and maximum concentration of 10 µg/L (Brenner 2010). 1,1,1-Trichloroethane was not detected at elevated concentrations or at a high frequency, and its degradation products were found at lower concentrations in the groundwater and thus was not used as vapor intrusion tracers. 1,1,1-Trichloroethane was detected in 99.6% of samples of indoor ambient air and in all samples of outdoor ambient air and outdoor background air (Brenner 2010). The mean concentrations of 1,1,1-trichloroethane were 0.212 µg/m^3 in indoor air, 0.185 µg/m^3 in outdoor air, and 0.182 µg/m^3 in outdoor background air (Brenner 2010).

A review of vapor intrusion data from 148 ATSDR public health assessments completed between 1994 and 2009 identified 36 sites with detected concentrations of 1,1,1-trichloroethane in groundwater, soil gas, or air (Burk and Zarus 2013). Indoor air was sampled at 15 of the sites with 1,1,1-trichloroethane detected from 0.03 to 200 µg/m^3, which are all below levels of health concern. Groundwater was sampled at 23 of the sites, and 3 of the sites had 1,1,1-trichloroethane concentrations at levels of concern for vapor intrusion. Two of the sites with elevated groundwater data (628,000 and 13,000 µg/L) did not have indoor air data, but the health assessments included recommendations to address exposures (ATSDR 2005a, 2006). The third site with elevated groundwater data (71,000 µg/L) had low indoor air detections up to 0.444 µg/m^3 in spring and summer, but ATSDR recommended follow-up sampling in winter

(ATSDR 2005b). None of the 36 sites were determined to be a public health hazard as a result of breathing 1,1,1-trichloroethane in indoor air from vapor intrusion.

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Since most applications and uses of 1,1,1-trichloroethane have been or are currently being discontinued, human exposure, while possible, is steadily decreasing. Airtight, highly-insulated houses are likely to have high indoor concentrations from use of household products containing 1,1,1-trichloroethane. However, the concentration of 1,1,1-trichloroethane has been shown to be higher in older homes, which may be less airtight and have higher rates of air exchange (Weisel et al. 2008). Very high levels of exposure are expected to occur for those who intentionally inhale 1,1,1-trichloroethane for its euphoric/ narcotic properties.

Workers who are still involved in processes using or disposing of this compound may encounter exposure to 1,1,1-trichlorethane. However, most occupational exposures are less likely to occur today as the production and use of 1,1,1-trichloroethane in the United States has been significantly reduced. A study of the association between kidney cancer and occupational exposure in individuals in Detroit and Chicago from 2002 to 2007 focused on solvent exposure found that 47 (4.4%) controls and 48 (4%) individuals with kidney cancer had a probability of exposure to 1,1,1-trichloroethane greater than 50% (Purdue et al. 2017). The most common task involving 1,1,1-trichloroehthane was degreasing, with 80% of participants involved in degreasing having at least 50% exposure probability (Purdue et al. 2017). Hein et al. (2010) used a database of air concentrations and associated exposure determinants in the United States to estimate the intensity of occupational exposure to 1,1,1-trichloroethane and two other solvents from 1940 to 2001. 1,1,1-Trichloroethane was most frequently released to the air via evaporation (Hein et al. 2010). Industrial mechanical dilution ventilation (mixing indoor air using fans or recirculation) decreased levels of 1,1,1-trichloroethane by 50%, and working outdoors was associated with 1,1,1-trichloroethane levels 90–95% lower than working indoors (Hein et al. 2010). Thus, people who worked indoors with 1,1,1-trichloroethane without ventilation were at higher risk of exposure. The 947 reported levels from the measurement database for 1,1,1-trichloroethane ranged from 0.0004 to 1,500 ppm, with a median of 0.95 ppm (Hein et al. 2010).

Workers in the iron and steel industry may be at higher risk of 1,1,1-trichloroethane exposure. Workplace air samples from sintering, coke making, and hot and cold forming processes were analyzed for VOCs (Chang et al. 2010). In the sintering process, 1,1,1-trichloroethane was detected at concentrations ranging

from 5.6 to 50 ppb (Chang et al. 2010). Small amounts of 1,1,1-trichloroethane were detected in the cakemaking process (Chang et al. 2010).

1,1,1-Trichloroethane was used in some adhesive remover pads of incubators in intensive care nurseries, and there is evidence that infants in incubators were exposed to high concentrations of 1,1,1-trichloroethane (Gallagher and Kurt 1990). This use of 1,1,1-trichloroethane has been discontinued. There are no existing studies that have monitored the level of exposure from 1,1,1-trichloroethane to children. Most uses of 1,1,1-trichloroethane are associated with occupational purposes, so it is unlikely that children will receive significant doses. Children may be exposed to 1,1,1-trichloroethane by playing near sources or through accidental ingestion or inhalation of the chemical.

CHAPTER 6. ADEQUACY OF THE DATABASE

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

Data needs are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.1 EXISTING INFORMATION ON HEALTH EFFECTS

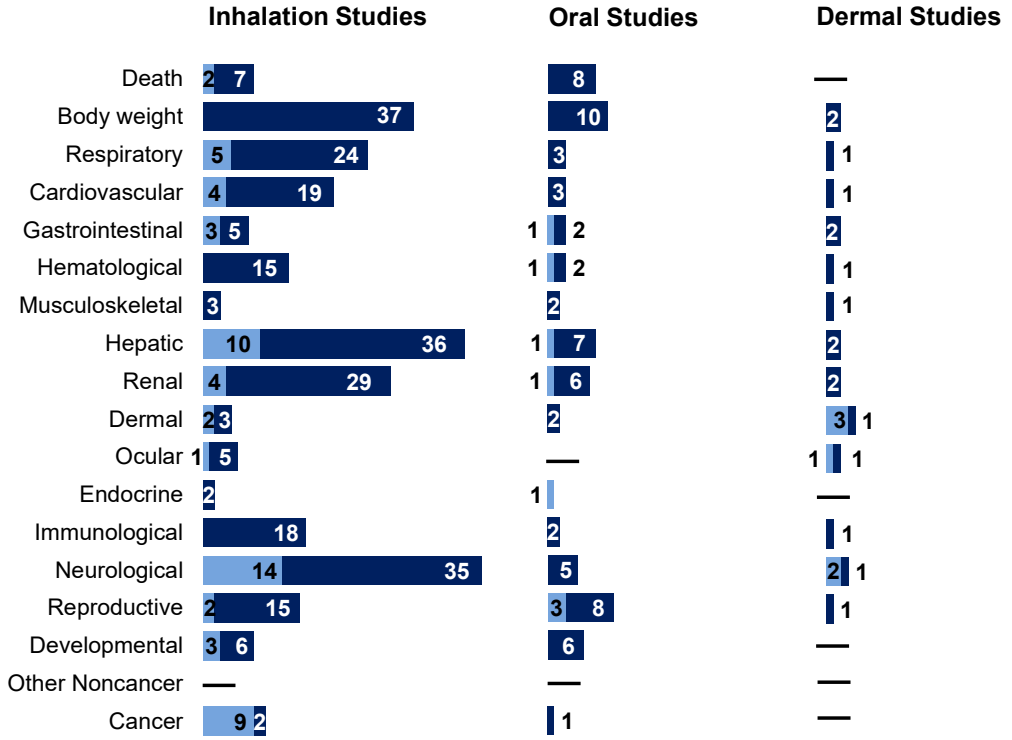
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to 1,1,1-trichloroethane that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of 1,1,1-trichloroethane. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies.

Several case studies have documented the lethality of high concentrations of inhaled 1,1,1-trichloroethane in humans. Experimental studies in humans, as well as case reports, have reported on acute systemic and neurological effects. Chronic neurological, developmental, reproductive, and cancer effects have been investigated in epidemiology studies. The available evidence in humans points to predominantly neurological effects after inhalation exposure to 1,1,1-trichloroethane, although case studies suggest that death may occur at sufficiently high doses. Carcinogenicity has been studied by a large number of case-control and a few cohort studies, with the vast majority of the studies showing no relationship between many types of cancer and prior exposure to 1,1,1-trichloroethane. However, two studies found a statistically significant relationship between 1,1,1-trichloroethane exposure and multiple myeloma, and one study found a relationship between 1,1,1-trichloroethane exposure and cancer of the nervous system (Anttila et al. 1995; Gold et al. 2011). Health effects caused by the oral and dermal routes of administration have not been as well studied in humans. One case study regarding oral exposure to 1,1,1-trichloroethane reported acute systemic effects and investigated potential neurological effects.

Figure 6-1. Summary of Existing Health Effects Studies on 1,1,1-Trichloroethane by Route and Endpoint*

Potential neurological, hepatic, body weight, renal, and respiratory effects were the most studied endpoints

The majority of the studies examined inhalation exposure in **animals** (versus **humans**)



*Includes studies discussed in Chapter 2, including those finding no effect. Most studies examined multiple endpoints.

Developmental effects and cancer from exposure to drinking water were investigated by epidemiology studies. The effects of dermal exposure are discussed in case reports regarding peripheral neuropathy and dermal sensitization in workers and in controlled studies regarding skin irritation.

6.2 IDENTIFICATION OF DATA NEEDS

Missing information in Figure 6-1 should not 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.

Because 1,1,1-trichloroethane is volatile and was used as a solvent in many products, it was most frequently found in the air in occupational settings due to volatilization during production and use. As such, inhalation exposures and toxicity are of primary concern and have been the most studied route of exposure to 1,1,1-trichloroethane. Under Section 604 of the Clean Air Act as amended in 1990, all production and use of 1,1,1-trichloroethane was scheduled to cease as of January 1, 2002. However, while production of 1,1,1-trichloroethane has decreased, it does continue and some facilities still report production and use of 1,1,1-trichloroethane to TRI and CDR. While present-day exposure is less likely, it is still possible. The oral and dermal routes of exposure were less of a potential exposure concern as the predominant fate in the environment is volatilization to the atmosphere, making inhalation the main route of exposure. Researcher consideration of likely routes of exposure may account for the comparatively lower number of publications on oral and dermal exposure to 1,1,1-trichloroethane. Differences in absorption, distribution, and metabolic pathways could lead to differences in toxic response and different target organs following the three routes of exposure.

Acute-Duration MRLs. Data from inhalation studies in humans based on decreased psychomotor performance were sufficient to derive an acute-duration inhalation MRL (Mackay et al. 1987). An acute-duration oral MRL was not derived due to lack of adequate data. The effects of acute-duration oral exposure of 1,1,1-trichloroethane have not been well studied. Six acute oral exposure studies were reported in four publications: two studies reporting LC_{50} data in mice and guinea pigs (Torkelson et al. 1958) and four studies that only evaluated a few toxicity endpoints (Bruckner et al. 2001; Platt and Cockrill 1969; Spencer et al. 1990). None of the available studies examined comprehensive toxicological

endpoints. Acute-duration oral studies evaluating comprehensive endpoints may provide data to derive an acute-duration oral MRL.

Intermediate-Duration MRLs. An intermediate-duration inhalation MRL was derived based on neurotoxicity (increase in GFAP, indicative of astroglioisis) in gerbils (Rosengren et al. 1985). An intermediate-duration oral MRL was developed based on reduced body weight gain in female mice data from the NTP (2000) oral study. While an oral MRL was developed, additional data for other intermediate-duration oral endpoints are lacking. Oral studies designed to assess more subtle neurological effects in animals exposed to 1,1,1-trichloroethane via the oral exposure route may be beneficial. Both NOAEL and LOAEL data are lacking for dermal exposures and since populations residing near hazardous waste sites may be potentially exposed to 1,1,1-trichloroethane, intermediate-duration dermal studies designed to determine values for systemic and other neurological effects would be valuable. An additional useful approach may be to develop route-to-route extrapolation using the existing inhalation PBPK models to assess the health risk from intermediate-duration oral or dermal exposure to 1,1,1-trichloroethane.

Chronic-Duration MRLs. MRL values were not derived for chronic-duration inhalation exposures because the most sensitive effect found in studies is represented by a serious effect; a chronic-duration oral MRL was not derived due to lack of adequate data. Since data needed to develop chronic-duration MRLs are lacking and since residents living near hazardous waste sites may be potentially exposed to 1,1,1-trichloroethane, studies that attempt to identify target organs and effect levels for all three exposure routes would be beneficial. Additionally, chronic-duration inhalation studies at doses <201 ppm could provide additional information regarding hepatic health effects and if they produce foci of hepatic changes, as this level of exposure in female mice led to hepatocellular adenomas/carcinomas, which is considered a serious effect.

Health Effects

Hepatic. Ohnishi et al. (2013) conducted a 2-year cancer bioassay following inhalation exposure. An increase in the occurrence of hepatocellular adenomas in female mice was observed at 201 ppm. However, as adenomas are considered serious effects, a data need has been identified to study hepatic effects of chronic-duration inhalation exposure to 1,1,1-trichloroethane in mice at doses <201 ppm. Conducting chronic-duration inhalation studies with lower concentrations would allow for a more definitive assessment of the minimum levels at which less serious hepatic effects occur after chronic-duration inhalation of 1,1,1-trichloroethane.

Immunological. No studies were identified regarding the immunotoxicity of 1,1,1-trichloroethane in humans and limited information regarding immunotoxicity was available for animals. The only human information available was a report of spleen congestion in subjects acutely exposed to high levels of 1,1,1-trichloroethane (Gresham and Treip 1983; Stahl et al. 1969). A single inhalation exposure to 1,1,1-trichloroethane in mice did not result in an increase in susceptibility to bacterial infection in exposed mice compared to controls (Aranyi et al. 1986). Very limited information exists regarding histology and function of tissues of the lymphoreticular system after 1,1,1-trichloroethane exposure by any route. Histological evaluation of lymph nodes, thymus, and spleen revealed no lesions attributable to 1,1,1-trichloroethane exposure (Adams et al. 1950; Calhoun et al. 1981; Kjellstrand et al. 1985b; Prendergast et al. 1967; Torkelson et al. 1958).

Although available studies do not suggest that 1,1,1-trichloroethane induces immunotoxicity, acute- and intermediate-duration inhalation and oral exposure studies evaluating potential immunotoxicity would provide valuable information regarding potential immunotoxicity.

Neurological. The central nervous system is apparently the primary target organ of 1,1,1-trichloroethane toxicity. In both animal and human studies, behavioral effects, altered electroencephalogram recordings, ataxia, unconsciousness, and death have been reported (Balster et al. 1982, 1997; Bowen and Balster 1996, 1998; Bruckner et al. 2001; Clark and Tinston 1982; De Ceaurriz et al. 1983; del Amo et al. 1996; Evans and Balster 1993; Gamberale and Hultengren 1973; Garnier et al. 1991; Gehring 1968; Kelafant et al. 1994; Mackay et al. 1987; Mattsson et al. 1993; Moser and Balster 1985, 1986; Muttray et al. 2000; Páez-Martínez et al. 2003; Spencer et al. 1990; Stewart et al. 1961, 1969; Sullivan 1994; Torkelson et al. 1958; Warren et al. 1997, 1998; Wiley et al. 2002; Winek et al. 1997; Woolverton and Balster 1981; You et al. 1994). Prolonged inhalation exposure to 1,1,1-trichloroethane in gerbils resulted in neurochemical changes suggested of morphological damage to the brain (Rosengren et al. 1985). Inhalation exposure has resulted in respiratory depression that appears to cause death in humans and animals. There are limited data on adverse effects following oral exposure. Neurological effects were not reported in the offspring of rats treated during gestation and lactation (Dow Chemical 1993) (see Developmental Toxicity). Neurological effects have not been reported after dermal exposure.

Studies designed to evaluate the impact of 1,1,1-trichloroethane exposure on neurological structure and function might provide important information regarding the mechanisms and reversibility of 1,1,1-trichloroethane induced neurological dysfunction. Additional studies on the reported changes in GFAP following 1,1,1-trichloroethane exposure may be helpful. Since information is lacking on the effects of 1,1,1-trichloroethane exposure via the oral route, acute-, intermediate-, and chronic-duration exposure studies designed to evaluate the impacts on the nervous system would provide information regarding the dose-response relationship for this route of exposure. Although available toxicokinetic data do not suggest route-specific target organs, an acute-duration dermal exposure study designed to assess the potential for neurotoxicity by this route would also be useful. In addition, using existing inhalation and oral data in PBPK models and extrapolating to dermal exposure might be a useful approach to assessing the risk of adverse neurological effects following dermal exposure to 1,1,1-trichloroethane. Epidemiological studies of potentially exposed populations, such as those living adjacent to hazardous waste sites or workers in occupational settings, may provide useful information on the potential for 1,1,1-trichloroethane at relevant exposure levels to produce neurological changes in humans.

Reproductive. An epidemiology study of fathers who were occupationally exposed to 1,1,1-trichloroethane during spermatogenesis found no relationship with adverse pregnancy outcomes (Taskinen et al. 1989). Limited information regarding reproductive toxicity in animals was located. Lane et al. (1982) found no reproductive effects in a multigeneration reproduction study of rats exposed to 1,1,1-trichloroethane in drinking water. Data from animal reproductive studies show mixed results. Several studies performing histological evaluations of reproductive organs and tissues in rats did not find lesions after inhalation exposure to 1,1,1-trichloroethane (Adams et al. 1950; Calhoun et al. 1981; Eben and Kimmerle 1974; Quast et al. 1988; Torkelson et al. 1958; Truffert et al. 1977). However, testicular degeneration was observed in guinea pigs exposed to 1,1,1-trichloroethane vapors (Adams et al. 1950). While NTP (2000) noted reduced epididymal spermatozoa concentration in male rats and mice administered 1,1,1-trichloroethane in the diet at a concentration of 80,000 ppm (approximate doses of 4,800 and 15,000 mg/kg/day, respectively) for 13 weeks, there were no other indications of adverse male reproductive effects and no signs of altered estrus in similarly treated female rats and mice (NTP 2000). No studies on the effects of 1,1,1-trichloroethane on reproductive function in humans were identified. As noted above, histopathological effects on reproductive organs have been observed animals but reproductive function (e.g., 2-generation reproduction studies) has not been assessed in animals after inhalation or dermal exposure to 1,1,1-trichloroethane. Although results of available studies

do not suggest route-specific target organs, an inhalation study of reproductive function in animals would be particularly valuable since inhalation is the predominant route of exposure in humans.

Developmental. The results from human epidemiological studies found no relationship between maternal exposure to 1,1,1-trichloroethane and adverse pregnancy outcomes, such as spontaneous abortions/congenital malformations (Deane et al. 1989; Lindbohm et al. 1990; Swan et al. 1989; Taskinen et al. 1989; Wrensch et al. 1990a, 1990b). Some studies in animals indicate that 1,1,1-trichloroethane is a potential developmental toxicant in high doses. Skeletal abnormalities such as delayed ossification and extra ribs in rats and rabbits, respectively, and decreased fetal body weight in rats have been reported after inhalation exposure of pregnant rats or rabbits during major organogenesis (BRRC 1987a, 1987b; York et al. 1982). However, two of the studies used concentrations that produced significant maternal toxicity (BRRC 1987a, 1987b). Late-stage gestational exposure to 1,1,1-trichloroethane vapors at concentrations that did not result in maternal toxicity, resulted in developmental milestone delays (pinnae detachment, incisor eruption, and eye opening) and impaired performance in neurobehavior tests were noted in mouse pups of dams (Jones et al. 1996). Neurological effects were not reported in the offspring of rats gavaged with 1,1,1-trichloroethane during gestation and lactation (Dow Chemical 1993). No teratogenic effects were reported in a multigeneration developmental study of oral 1,1,1-trichloroethane exposure in rats (Lane et al. 1982). Since dermal data are lacking, route-to-route extrapolation of existing inhalation and oral data using PBPK models might be a useful approach to assessing the risk of adverse developmental effects from dermal exposure to 1,1,1-trichloroethane. Additional developmental toxicity studies of inhalation or oral 1,1,1-trichloroethane exposure that investigate neurological effects at lower doses of exposure might be useful.

Cancer. Maltoni et al. (1986) conducted 2-year cancer bioassays following both inhalation and oral exposure. An increase in the occurrence of immunoblastic lymphosarcoma was reported in rats following oral exposure. However, the following limitations of the study preclude the drawing of definitive conclusions: only one dose level was used, only a small number of rats responded, and experimental procedures were compromised. No effects were reported in a well-designed inhalation study at exposure levels ≤1,500 ppm (Quast et al. 1988). Conducting inhalation studies with higher concentrations, conducting oral studies using several dose levels,

using larger study groups, and using more than one species would allow for a more definitive assessment of the carcinogenic potential of 1,1,1-trichloroethane.

Genotoxicity. No studies were identified regarding the genotoxic potential of 1,1,1-trichloroethane in humans. Genotoxicity studies indicate that 1,1,1-trichloroethane may be weakly mutagenic in *Salmonella* (Gocke et al. 1981; Nestmann et al. 1980, 1984; Simmon et al. 1977), induce deletions via intrachromosomal recombination in *Saccharomyces cerevisiae* (Brennan and Schiestl 1998), transform mammalian cells *in vitro* (Daniel and Dehnel 1981; Hatch et al. 1982, 1983; Milman et al. 1988; Price et al. 1978; Tu et al. 1985), and form DNA adducts in the mouse liver *in vivo* (Turina et al. 1986). While studies of other genotoxic effects have mostly been negative, most were not designed to prevent the volatilization of 1,1,1-trichloroethane, which likely resulted in lower than planned for exposures. Studies designed to prevent the loss of 1,1,1-trichloroethane through volatilization would allow genotoxic effects to be more accurately assessed. Additionally, both tests of chromosomal aberrations in peripheral lymphocytes from humans known to have been exposed to 1,1,1-trichloroethane and genotoxicity testing of 1,1,1-trichloroethane metabolites might be useful.

Epidemiology and Human Dosimetry Studies. No health effects associated with exposure to 1,1,1-trichloroethane have been reported for reproductive, developmental, or cancer endpoints in humans. However, these epidemiological studies are limited in design and scope, which limits their usefulness in ascertaining health effects from 1,1,1-trichloroethane exposure. Conducting well-designed epidemiological studies might provide a definitive assessment of the health hazards of chronic-duration 1,1,1-trichloroethane exposure, especially for occupationally exposed populations. Human dosimetry studies may be able to correlate 1,1,1-trichloroethane levels in human tissues or fluids with chronic health effects. Chronic-duration studies of populations living near hazardous waste sites may not be useful because exposures are likely low and the half-lives of 1,1,1-trichloroethane and its metabolites are short. Neurological effects have been demonstrated in humans following acute-duration inhalation exposures. Although potentially exposed subpopulations exist, potential nonoccupational exposure is expected to be reduced due to Title VI of the Clean Air Act.

Biomarkers of Exposure and Effect. Biomarkers of 1,1,1-trichloroethane exposure include blood, breath, and urine levels of the chemical and its two major metabolites, trichloroethanol and trichloroacetic acid. However, the two major metabolites of 1,1,1-trichloroethane are also metabolites of trichloroethylene and perchloroethylene and may therefore not indicate exposure to 1,1,1-trichloroethane

specifically (Monster 1988). Several studies report that environmental 1,1,1-trichloroethane levels are significantly correlated with the blood, breath, and urine levels (Hartwell et al. 1987; Mizunuma et al. 1995; Monster 1986; Wallace et al. 1982, 1984, 1985, 1987a, 1987b, 1987c). While 1,1,1-trichloroethane is rapidly cleared from the body after exposure (Astrand et al. 1973; Monster et al. 1979; Nolan et al. 1984; Stewart et al. 1961), the two metabolites have a much longer half-life in the body than the parent compound. Therefore, 1,1,1-trichloroethane levels in the blood, breath, and urine may be used as biomarkers only if they are measured during or shortly after exposure, whereas the two metabolites may be more useful as biomarkers for a somewhat longer period after exposure; however, they could also indicate exposure to trichloroethylene and perchloroethylene.

No specific biomarkers of effect, including hematological and clinical chemistry parameters, for 1,1,1-trichloroethane were found in the literature. However, since the central nervous system is apparently the most sensitive organ in humans and animals, and neurotoxicity (decreased psychomotor performance, ataxia, and unconsciousness) is observed after short-term high-level exposure, identification of biomarkers of effect may be useful.

Absorption, Distribution, Metabolism, and Excretion. While the absorption, metabolism, and elimination of 1,1,1-trichloroethane have been studied extensively in humans and animals, distribution has not been as well studied. Absorption of 1,1,1-trichloroethane by the lung, skin (under conditions to prevent evaporation), and gastrointestinal tract of humans and animals is rapid and efficient (Astrand et al. 1973; Fukabori et al. 1977; Kezic et al. 2000, 2001; Monster et al. 1979; Nolan et al. 1984; Reitz et al. 1988; RTI 1987; Stewart and Andrews 1966; Stewart and Dodd 1964; Tsuruta 1975). Because 1,1,1-trichloroethane is metabolized at a low rate and steady-state levels in the blood and tissues are reached, the percentage net absorption decreases with increasing inhalation duration. A study with humans equipped with respirators exposed to 1,1,1-trichloroethane vapors in the atmosphere reported that absorbed doses from inhaled 1,1,1-trichloroethane are much larger than doses from dermal absorption (Riihimäki and Pfäffli 1978). In animals 1,1,1-trichloroethane is distributed by the blood to the tissues and organs with preferential distribution to fatty tissues and is also distributed to developing fetuses (Holmberg et al. 1977; Katagiri et al. 1997; Schumann et al. 1982; Takahara 1986a). Human autopsy data from 30 cases reported detectable levels of 1,1,1-trichloroethane in subcutaneous fat, kidney fat, liver, lung, and muscle (Alles et al. 1988). Studies evaluating the effects of 1,1,1-trichloroethane on drug-metabolizing enzymes have conflicting results; additional studies to further define these effects would provide useful information. Regardless of exposure route, exhalation of 1,1,1-trichloroethane is the predominant pathway of elimination by humans and animals (Mitoma et al. 1985; Monster et al. 1979;

Nolan et al. 1984; Reitz et al. 1988; RTI 1987; Schumann et al. 1982). When exposure ceases, 1,1,1-trichloroethane rapidly clears from the body. Only trace amounts of 1,1,1-trichloroethane remained in animal tissues within days of short-term exposure. Since human dermal data are lacking, additional studies in humans that assess the extent and rates of absorption and elimination with dermal exposure to aqueous 1,1,1-trichloroethane solutions or suspensions under conditions allowing evaporation from the skin may provide useful information on dermal contact with contaminated water.

The hepatotoxicity of 1,1,1-trichloroethane is quite low compared to other chlorinated hydrocarbons, including 1,1,2-trichloroethane. The more hepatotoxic halocarbons are extensively metabolized, whereas 1,1,1-trichloroethane has a low rate of metabolism. Whether the mild effects of repeated 1,1,1-trichloroethane exposure are evoked by the parent compound or the limited quantities of metabolites produced is not known. However, the acute effects on central nervous and cardiovascular systems are reportedly caused by 1,1,1-trichloroethane and not its metabolites. The reported acute effects on membrane-mediated processes are due to the lipophilicity of 1,1,1-trichloroethane. Several cellular and biochemical processes appear to be affected by 1,1,1-trichloroethane. Sufficient data exist for absorption, metabolism, and elimination of 1,1,1-trichloroethane and further studies do not appear necessary. The distribution of 1,1,1-trichloroethane has not been as extensively studied and may warrant further investigation.

Comparative Toxicokinetics. Although the toxicokinetic pattern of 1,1,1-trichloroethane is qualitatively similar in humans, rats, and mice, there are major quantitative differences, including a higher blood:air partition coefficient, higher respiratory and circulatory rates, and increased rate of metabolism in mice, indicating that rats may be a better model for humans than mice. PBPK models have been developed to describe the kinetic behavior of 1,1,1-trichloroethane in mice, rats, and humans and have been used to estimate exposure levels that either produce or don't produce toxic effects in humans using interspecies and inter-route extrapolation methods (Bogen and Hall 1989; Dallas et al. 1989; Dobrev et al. 2001, 2002; Leung 1992; Nolan et al. 1984; Poet et al. 2000; Reitz et al. 1988). Further research verifying the metabolic constants and other input parameters used in these models might improve the accuracy and utility of the models in interspecies extrapolations. In addition, verification of the models at lower doses could provide relevant information.

Children's Susceptibility. Data needs related to both prenatal and childhood exposures, and developmental effects expressed whether prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above. No information was located regarding potential age-related differences in susceptibility to 1,1,1-trichloroethane in humans. One animal study in mouse pups of dams

exposed to 1,1,1-trichloroethane vapors in the later stages of gestation reported delays in developmental milestones and impaired performance in neurobehavior tests (Jones et al. 1996). These results suggest that developing organisms may be more susceptible than adults to the toxic effects of 1,1,1-trichloroethane (Schumann et al. 1982). Additional well-designed animal studies could assess the potential for age-related increased susceptibility to 1,1,1-trichloroethane.

Physical and Chemical Properties. The physical and chemical properties of 1,1,1-trichloroethane are well documented, and additional information in this area does not appear necessary. Only one BCF for 1,1,1-trichloroethane was located in the available literature (Barrows et al. 1980). This value is, however, consistent with what would be expected based on the other physical and chemical properties of 1,1,1-trichloroethane.

Production, Import/Export, Use, Release, and Disposal. Data on facilities producing 1,1,1-trichloroethane and on releases of 1,1,1-trichloroethane to the air, soil, and water are available through the TRI. Data on the historical uses and production of 1,1,1-trichloroethane are available in the literature. There is uncertainty regarding current domestic production of 1,1,1-trichloroethane. The CDR lists production volumes for years 2016–2019; however, the only domestic production is expected to be for export purposes to developing countries. The USITC has not shown import or export volumes since 2014. While methods of disposal are available in the literature and regulations on the disposal of 1,1,1-trichloroethane exist, information of the amount of 1,1,1-trichloroethane disposed of is lacking.

Environmental Fate. Data on the environmental fate of 1,1,1-trichloroethane are well represented in the literature. The partitioning of 1,1,1-trichloroethane from soil or water to the atmosphere is well established, and there is sufficient evidence to indicate that the compound can leach into groundwater (Lyman et al. 1990; Swann et al. 1983). The relatively slow rate of degradation and the major routes of 1,1,1-trichloroethane degradation in all environmental compartments have been established. The relatively long persistence of 1,1,1-trichloroethane in the atmosphere indicates that a significant portion of this compound migrates to the stratosphere (Prinn et al. 1987; Singh et al. 1992). Data on the biodegradation of 1,1,1-trichloroethane in soil are lacking. Additional data regarding the environmental fate of 1,1,1-trichloroethane do not appear necessary.

Bioavailability from Environmental Media. Numerous toxicokinetic and toxicity studies in humans and animals have demonstrated the bioavailability of 1,1,1-trichloroethane from air and drinking water. Although some data on the bioavailability of 1,1,1-trichloroethane from air to mammalian skin (Mattie et

al. 1994), and from air to other mammalian tissues (blood, muscle, liver) (Connell et al. 1993) are available, no studies on the bioavailability of 1,1,1-trichloroethane from food or soil were identified. Some of the important routes of exposure to 1,1,1-trichloroethane for residents near waste sites will be inhalation of airborne dusts, ingestion of soil (children), and dermal contact with contaminated soil (mostly children). Therefore, it would be helpful to develop reliable data for the bioavailability of 1,1,1-trichloroethane from dust as a result of inhalation of contaminated airborne dust, from soil as a result of ingestion of soil, and from soil as a result of dermal contact with soil.

Food Chain Bioaccumulation. 1,1,1-Trichloroethane is not believed to bioconcentrate in fish and aquatic organisms (Barrows et al. 1980); thus, it is not expected to biomagnify in the food chain. There are limited data regarding food chain biomagnification of 1,1,1-trichloroethane.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of 1,1,1-trichloroethane in contaminated media at hazardous waste sites are needed to assess the potential risk of exposure in populations living near hazardous waste sites. Recent monitoring data in water, soil, and sediment are available for 1,1,1-trichloroethane. More recent monitoring data for levels in air and other media, such as food, are needed to assess the exposure level for the general population.

Exposure Levels in Humans. 1,1,1-Trichloroethane has been detected in human tissues and expired air. NHANES monitors 1,1,1-trichloroethane in the blood of the U.S. population, and the data indicate that it is present at very low to undetectable levels. This is consistent with expected values, since 1,1,1-trichloroethane use and production has been phased down and has therefore decreased in the United States.

Exposures of Children. No studies were identified that measured the level of 1,1,1-trichloroethane exposures of children. It is expected that exposure will be insignificant. If exposure does occur, it is likely to be through playing near contaminated sources or through accidental ingestion or inhalation. However, more information is needed to accurately assess the potential of 1,1,1-trichloroethane exposure of children.

6.3 ONGOING STUDIES

No ongoing studies were identified in the National Institute of Health (NIH) RePORTER (2023) database.

CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding 1,1,1-trichloroethane in air, water, and other media are summarized in Table 7-1. This table is not an exhaustive list, and current regulations should be verified by the appropriate regulatory agency.

ATSDR develops MRLs, which are substance-specific guidelines intended to serve as screening levels by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. See Section 1.3 and Appendix A for detailed information on the MRLs for 1,1,1-trichloroethane.

Table 7-1. Regulations and Guidelines Applicable to 1,1,1-Trichloroethane

Agency	Description	Information	Reference
	Air		
EPA	RfC		IRIS 2007
	Acute RfCs		
	1 hour	9 mg/m^3 (1.6 ppm)	
	4 hours and 8 hours	7 mg/m^3 (1.3 ppm)	
	24 hours	6 mg/m^3 (1.1 ppm)	
	Short-term RfC	5 mg/m^3 (0.9 ppm)	
	Subchronic RfC	5 mg/m^3 (0.9 ppm)	
	Chronic RfC	5 mg/m^3 (0.9 ppm)	
WHO	Air quality guidelines	No data	WHO 2010
	Water & Food		
EPA	Drinking water standards and health advisories		EPA 2018a
	1-Day health advisory (10-kg child)	100 mg/L	
	10-Day health advisory (10-kg child)	40 mg/L	
	DWEL[a]	70 mg/L	
	National primary drinking water regulations		EPA 2009
	MCL	0.2 mg/L	
	MCLG	0.2 mg/L	
	RfD		IRIS 2007
	Chronic RfD	2 mg/kg/day	
	Subchronic RfD	7 mg/kg/day	

Table 7-1. Regulations and Guidelines Applicable to 1,1,1-Trichloroethane

Agency	Description	Information	Reference
WHO	Drinking water quality guidelines	Not established	WHO 2022
FDA	Substances added to food (formerly EAFUS)	Not listed	FDA 2023
	Allowable level in bottled water	0.20 mg/L	FDA 2022
	Cancer		
HHS	Carcinogenicity classification	No data	NTP 2021
EPA	Carcinogenicity classification	No data[b]	IRIS 2007
IARC	Carcinogenicity classification	Group 2A[c]	IARC 2022
	Occupational		
OSHA	PEL (8-hour TWA) for general industry, construction, and shipyards	350 ppm (1,900 mg/m^3)	OSHA 2021a, 2021b, 2021c
NIOSH	15-minute ceiling REL	350 ppm (1,900 mg/m^3)[d]	NIOSH 2019
	Emergency Criteria		
NIOSH	IDLH	700 ppm	NIOSH 2019
EPA	AEGLs-air		EPA 2018c
	AEGL 1[e]		
	10-minute, 30-minute, 60-minute, 4-hour, 8-hour	230 ppm	
	AEGL 2[e]		
	10-minute	930 ppm	
	30-minute	670 ppm	
	60-minute	600 ppm	
	4-hour	380 ppm	
	8-hour	310 ppm	
	AEGL 3[e]		
	10-minute	4,200 ppm	
	30-minute	4,200 ppm	
	60-minute	4,200 ppm	
	4-hour	2,700 ppm	
	8-hour	2,100 ppm	

Table 7-1. Regulations and Guidelines Applicable to 1,1,1-Trichloroethane

Agency	Description	Information	Reference
DOE	PACs-air		DOE 2000
	PAC-1[f]	230 ppm	
	PAC-2[f]	600 ppm	
	PAC-3[f]	4,200 ppm	

[a]DWEL: A lifetime exposure level, assuming 100% exposure from drinking water, at which adverse, noncarcinogenic health effects would not be expected to occur.
[b]Inadequate information to assess carcinogenic potential.
[c]Group 2A: probably carcinogenic to humans.
[d]NIOSH recommends that 1,1,1-trichloroethane be treated in the workplace with caution because of its structural similarity to four chloroethanes shown to be carcinogenic in animals (NIOSH 2018).
[e]Definitions of AEGL terminology are available from EPA (2018b).
[f]Definitions of PAC terminology are available from DOE (2023).

AEGL = acute exposure guideline level; DOE = Department of Energy; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; MCLG = maximum contaminant level goal; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TWA = time-weighted average; WHO = World Health Organization

CHAPTER 8. REFERENCES

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APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure. MRLs are based on noncancer health effects only; cancer effects are not considered. 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 NOAEL/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) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. LOAELs for serious health effects (such as irreparable damage to the liver or kidneys, or serious birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substances than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

APPENDIX A

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Office of Innovation and Analytics, Toxicology Section, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Office of Innovation and Analytics, Toxicology Section, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S106-5, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,1,1-Trichloroethane
CAS Numbers: 71-55-6
Date: March 2024
Profile Status: Final
Route: Inhalation
Duration: Acute
MRL: 1 ppm (6 mg/m^3)
Critical Effect: Neurological endpoint of decreased performance in psychomotor tests
Reference: Mackay et al. 1987
Point of Departure: LOAEL of 175 ppm (950 mg/m^3); $LOAEL_{ADJ}$ of 119 ppm (650 mg/m^3)
Uncertainty Factor: 100
LSE Graph Key: 3
Species: Human

MRL Summary: An acute-duration inhalation MRL of 1 ppm (6 mg/m^3) was derived for 1,1,1-trichloroethane based on a neurological endpoint of decreased performance in psychomotor tests in humans administered 1,1,1-trichloroethane via inhalation (Mackay et al. 1987). The MRL is based on a LOAEL of 175 ppm, which was applied to a PBPK model to estimate the 24-hour continuous exposure concentration for exposed humans that would result in the same estimated internal dose. This resulted in an adjusted LOAEL of 119 ppm, which was then divided by a total uncertainty factor of 100 (10 for the use of a LOAEL and 10 for human variability).

Selection of the Critical Effect: A number of studies have evaluated the toxicity of 1,1,1-trichloroethane following acute-duration inhalation exposure, although the majority of the studies with more sensitive endpoints focused on neurological endpoints (Evans and Balster 1993; Gamberale and Hultengren 1973; Mackay et al. 1987; Nilsson 1986b; NIOSH 1975; Stewart et al. 1969). Evans and Balster (1993) observed convulsions in mice after 4 days of 24 hour/day exposure to 500 ppm 1,1,1-trichloroethane, which is regarded as a serious effect. Thus, only effects observed at concentrations <500 ppm were considered for the critical effect. Nilsson (1986b) observed a reduction in brain cyclic guanosine monophosphate (cGMP) at 100 ppm, although these results were only presented graphically and were observed in a mouse model rather than in a human. Human studies are generally preferred to animal studies when available, and both Gamberale and Hultengren (1973) and Mackay et al. (1987) were studies conducted in humans. The data from these human studies suggest that decreased performance in psychomotor tests is the most sensitive endpoint following acute-duration inhalation exposure. A summary of select LOAELs is presented in Table A-1.

Table A-1. Summary of Relevant NOAEL and LOAEL Values Following Acute-Duration Inhalation Exposure to 1,1,1-Trichloroethane

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Neurological effects					
Human	4 exposures 30 minutes/exposure	239.2	338.3	12.8% decrease in reaction time, 22.6% decrease in perceptual speed, 9.8% decrease in manual dexterity	Gamberale and Hultengren 1973
Human	3.5 hours		175	10–15% decrease in simple reaction time	Mackay et al. 1987

Table A-1. Summary of Relevant NOAEL and LOAEL Values Following Acute-Duration Inhalation Exposure to 1,1,1-Trichloroethane

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Mouse NS	4 hours	50	100	~33% decrease in brain cGMP	Nilsson 1986b

cGMP = cyclic guanosine monophosphate; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; NS = not specified

Selection of the Principal Study: Mackay et al. (1987) evaluated the neurological and toxicological effects of 1,1,1-trichloroethane inhalation in humans. The LOAEL reported by Mackay et al. (1987) for a 10–15% decrease in simple reaction time was the lowest among the studies evaluating acute-duration inhalation exposure in humans. The Mackay et al. (1987) study was also selected by the EPA for the derivation of an acute-duration inhalation reference concentration (RfC) for 1,1,1-trichloroethane. The same methodology used to derive the acute-duration inhalation RfC was used to derive the acute-duration inhalation MRL.

Summary of the Principal Study:

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

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

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

Selection of the Point of Departure for the MRL: The lowest concentration administered, 175 ppm (950 mg/m^3), is a LOAEL for neurobehavioral effects. Benchmark dose (BMD) modeling was unable to be performed adequately because the study authors did not provide standard deviations of the means with their results. EPA (2006) used a PBPK model by Reitz et al. (1988) to estimate the internal dose in humans exposed to 950 mg/m^3 1,1,1-trichloroethane for 1 hour. The estimated internal dose is 1.33 mg/L.

Adjustment for Intermittent Exposure: The Reitz et al. (1988) model was used to estimate the 24-hour continuous exposure concentration that achieves the estimated internal dose of 1.33 mg/L. The resulting $LOAEL_{ADJ}$ is 119 ppm (650 mg/m^3).

Uncertainty Factor: The $LOAEL_{ADJ}$ is divided by a total uncertainty factor of 100:

- 10 for use of a LOAEL
- 10 for human variability

MRL = LOAEL ÷ uncertainty factors
119 ppm ÷ (10 x 10) = 1.19 ppm (6.497 mg/m^3) ≈ 1 ppm (6 mg/m^3)

Other Additional Studies or Pertinent Information that Lend Support to this MRL: EPA derived an acute-duration inhalation RfC for 1,1,1-trichloroethane of 1.1 ppm for a 24-hour exposure based on the Mackay et al. (1987) study. Gamberale and Hultengren (1973) observed psychophysiological test performance deficits in human subjects exposed to 250, 350, 450, and 550 ppm of 1,1,1-trichloroethane in consecutive 30-minute periods. All tasks tested were affected, including simple reaction time, choice reaction time, and tests for manual dexterity and perceptual speed. Statistically significant deficits were found as early as exposure period #2, during which the exposure concentration was 350 ppm. Muttray et al. (1999, 2000) found electroencephalogram changes consistent with increased drowsiness and slight irritant nasal responses in volunteers exposed to 200 ppm. In contrast, no psychomotor effects were seen in volunteers exposed to 1,1,1-trichloroethane vapors at concentrations of 400–450 ppm for 4 hours once or twice in a 24-hour period (Salvini et al. 1971; Savolainen et al. 1981). Laine et al. (1996) found no consistent, statistically significant effects on electroencephalogram, visual-evoked potential, or equilibrium in a group of nine healthy male volunteers exposed to a constant 200 ppm of 1,1,1-trichloroethane vapors for 3 hours, followed by a 40-minute lunch break and a 40-minute afternoon exposure. A conservative approach was followed in the selection of Mackay et al. (1987) as the critical study for derivation of an acute-duration inhalation MRL because it identified the lowest LOAEL for psychomotor effects in humans following acute-duration inhalation exposure to 1,1,1-trichloroethane and was supported by results of Gamberale and Hultengren (1973) and Muttray et al. (1999, 2000). The choice of critical effect (neurological changes) is supported by animal studies, although exposure levels eliciting neurobehavioral and neurophysiological effects were much higher than those eliciting psychomotor effects in humans. For example, increased motor activity was observed in mice exposed to 1,250 ppm of 1,1,1-trichloroethane for 30 minutes (Bowen and Balster 1996). A 4-hour exposure of mice to 2,064 ppm resulted in impaired swimming behavior (De Ceaurriz et al. 1983). Dow Chemical (1990) reported 1,1,1-trichloroethane-induced alterations in flash-evoked potential, somatosensory-evoked potential, and electroencephalogram in rats exposed to 1,000 ppm for 6 hours/day on 4 consecutive days.

Agency Contacts (Chemical Managers): Carolyn Harper

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,1,1-Trichloroethane
CAS Numbers: 71-55-6
Date: March 2024
Profile Status: Final
Route: Inhalation
Duration: Intermediate
MRL: 0.7 ppm (4 mg/m^3)
Critical Effect: Neurological endpoint of increased GFAP in brain indicative of neuronal damage
Reference: Rosengren et al. 1985
Point of Departure: NOAEL of 70 ppm
Uncertainty Factor: 100
LSE Graph Key: 74
Species: Gerbil

MRL Summary: An intermediate-duration inhalation MRL of 0.7 ppm (4 mg/m^3) was derived for 1,1,1-trichloroethane based on neurological endpoint of increased GFAP in gerbils administered 1,1,1-trichloroethane via continuous inhalation exposure (Rosengren et al. 1985). The MRL is based on a NOAEL of 70 ppm divided by a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

***Selection of the Critical Effect*:** A number of studies have evaluated the toxicity of 1,1,1-trichloroethane following intermediate-duration inhalation exposure. Prendergast et al. (1967) observed substantial reductions in body weight gain at 380 ppm for both dogs and rabbits when exposed 24 hours/day for 90 days. This exposure resulted in a 51% reduction in body weight gain for dogs and a 66% reduction in body weight gain for rabbits; both of these endpoints are classified as serious LOAELs. Thus, only two studies, Rosengren et al. (1985) and MacEwen and Vernot (1974), observed effects at concentrations <380 ppm; a summary of these LOAELs is presented in Table A-2.

Table A-2. Summary of Relevant NOAEL and LOAEL Values Following Intermediate-Duration Inhalation Exposure to 1,1,1-Trichloroethane

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Neurological effects					
Gerbil Mongolian	3 months 24 hours/day	70	210 (serious LOAEL)	20% increase in GFAP	Rosengren et al. 1985
Hepatic effects					
Mouse NS	14 weeks 24 hours/day		250	Fatty changes in the liver	MacEwen and Vernot 1974

GFAP = glial fibrillary acid protein; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; NS = not specified

The available data suggest that increased GFAP in the brain is the most sensitive endpoint following intermediate-duration inhalation exposure. In gerbils, a 20% increase in GFAP in the brain was seen at concentrations of 210–1,000 ppm, and a NOAEL of 70 ppm was observed (Rosengren et al. 1985).

Selection of the Principal Study: Rosengren et al. (1985) evaluated neurological and toxicological effects of 1,1,1-trichloroethane inhalation in humans. The NOAEL reported by Rosengren et al. (1985) for an increase in GFAP was the lowest among the studies evaluating intermediate-duration inhalation exposure.

Summary of the Principal Study:

Rosengren LE, Aurell A, Kjellstrand P, et al. 1985. Astrogliosis in the cerebral cortex of gerbils after long-term exposure to 1,1,1-trichloroethane. Scand J Work Environ Health 11:447-455.

Groups of Mongolian gerbils (four/sex) were exposed to 70, 210, or 1,000 ppm of 1,1,1-trichloroethane vapor (cleaning grade, containing 5% dioxane-free stabilizers) continuously for 3 months. Each exposure group was paired with a control group consisting of eight sex-matched littermates of the test group. At the end of the exposure period, all animals were held for 4 months prior to sacrifice. Upon sacrifice, brains were weighed and prepared for analyses for the astroglial proteins, S-100 and GFAP, both of which are biomarkers for astrogliosis. Astrogliosis is the activation of cellular processes in the central nervous system aimed at protecting and repairing damage to the brain in response to neural toxicity. Astrogliosis is generally accompanied by a rapid synthesis of GFAP (Eng et al. 2000); thus, an increase in GFAP is considered one of the first indicators of a deviation from normal physiology (Brahmachari et al. 2006).

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

Selection of the Point of Departure for the MRL: The lowest concentration administered, 70 ppm, is a NOAEL for neurotoxic effects. BMD modeling was not attempted as the data representing measurements of GFAP were not presented in a way that allowed for precise measurement of response.

Adjustment for Intermittent Exposure: As the gerbils in Rosengren et al. (1985) were continuously exposed for 3 months, there was no need to adjust for intermittent exposure. Therefore, the NOAEL of 70 ppm was not adjusted for exposure duration.

Uncertainty Factor: The NOAEL is divided by a total uncertainty factor of 100

- 10 for extrapolation from animals to humans
- 10 for human variability

MRL = NOAEL ÷ uncertainty factors
70 ÷ (10 x 10) = 0.7 ppm (4 mg/m^3)

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

strength in rats exposed to 2,000 ppm of 1,1,1-trichloroethane, 6 hours/day, 5 days/week for 13 weeks. Bowen and Balster (2006) observed a 166% increase in locomotor activity in mice exposed to 6,000 ppm of 1,1,1-trichloroethane, 30 minutes/day for 15 days.

Qualitative and quantitative analysis of GFAP has shown it to be a sensitive and specific indicator of gliosis, a hallmark feature of injury to the central nervous system (O'Callaghan and Sriram 2005). O'Callaghan and Sriram (2005) examined the effects of numerous known toxicants on GFAP and reported an increase in GFAP that is rapid, linked to the location of damage, and can occur at doses well below those associated with behavioral change. Although Rosengren et al. (1985) observed an increase in GFAP that was not accompanied by an increase in another marker of gliosis, S-100; there are no known or established relationships between changes in GFAP and changes in S-100 (O'Callaghan and Sriram 2005). This suggests that the increase in GFAP observed in Rosengren et al. (1985) is a valid indicator of neurotoxicity, even without additional neurotoxic or behavioral observations accompanying the change.

Agency Contacts (Chemical Managers): Carolyn Harper

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,1,1-Trichloroethane
CAS Numbers: 71-55-6
Date: March 2024
Profile Status: Final
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration inhalation MRL.

Rationale for Not Deriving an MRL: An MRL has not been derived for chronic-duration inhalation exposure to 1,1,1-trichloroethane because the database is insufficient. No adverse effects were observed in humans occupationally exposed to 1,1,1-trichloroethane at exposures up to 200 ppm (Kramer et al. 1978; Maroni et al. 1977). NOAELs and LOAELs for animals exposed chronically to inhaled 1,1,1-trichloroethane are summarized in Table A-3. The only noncancer endpoint observed in the chronic-duration inhalation database in animals was mild histopathological changes in the liver of rats exposed to 1,500 ppm 1,1,1-trichloroethane for 104 weeks (5 days/week, 6 hours/day), with a NOAEL of 500 ppm (Quast et al. 1988). However, no quantitative data or statistical analyses were reported regarding the incidence of hepatic lesions. Therefore, the Quast et al. (1988) study does not provide adequate information to serve as the principal study for derivation of the chronic-duration inhalation MRL. Other studies in rats and mice did not observe adverse effects at exposure levels up to 1,500 and 3,181 ppm, respectively (Ohnishi et al. 2013; Quast et al. 1988). The only other finding observed was hepatocellular adenoma in female mice at 201 ppm (Ohnishi et al. 2013); however, this effect cannot be used for derivation of the chronic-duration inhalation MRL because MRLs are based on noncancer endpoints. Therefore, a chronic-duration inhalation MRL for 1,1,1-trichloroethane was not derived.

Table A-3. Summary of NOAELs and LOAELs in Chronic-Duration Inhalation Studies on 1,1,1-Trichloroethane

Species	Duration/ route	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Hepatic effects					
Rat F344	104 weeks 5 days/week 6 hours/day	500	1,500	Mild liver histopathology (accentuation of the normal hepatic lobular pattern, alteration in the size of the hepatocytes)	Quast et al. 1988
Rat F344	104 weeks 5 days/week 6 hours/day	3,181			Ohnishi et al. 2013
Mouse B6C3F1	104 weeks 5 days/week 6 hours/day	1,500			Quast et al. 1988

Table A-3. Summary of NOAELs and LOAELs in Chronic-Duration Inhalation Studies on 1,1,1-Trichloroethane

Species	Duration/ route	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Mouse BDF1	104 weeks 5 days/week 6 hours/day		201 F (SLOAEL)	CEL: Hepatocellular adenoma	Ohnishi et al. 2013

Adjusted daily dose = $intermittent\ dose \times \frac{exposure\ hours}{24\ hours} \times \frac{exposure\ days}{7\ days}$

ADJ = adjusted; CEL = cancer effect level; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; SLOAEL: serious lowest-observed-adverse-effect level

Agency Contacts (Chemical Managers): Carolyn Harper

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,1,1-Trichloroethane
CAS Numbers: 71-55-6
Date: March 2024
Profile Status: Final
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration oral MRL due to insufficient information that could be used to identify sensitive endpoints.

Rationale for not deriving an MRL: An MRL has not been derived for acute-duration oral exposure (≤14 days) to 1,1,1-trichloroethane. The effects of acute-duration oral exposure of 1,1,1-trichloroethane have not been well studied. Six acute oral exposure studies were reported in four publications: two studies reporting LC_{50} data in mice and guinea pigs (Torkelson et al. 1958) and four studies that only evaluated a few toxicity endpoints (Bruckner et al. 2001; Platt and Cockrill 1969; Spencer et al. 1990). None of the available studies examined comprehensive toxicological endpoints. The lowest LOAEL was reported by Spencer et al. (1990) for neurological effects in female rats orally exposed to 705 mg/kg via gavage for 4 days; a NOAEL was not identified. Neurological effects were increased latency in flash-evoked potentials and a decrease in electroencephalogram at low power frequency. However, due to the lack of studies evaluating comprehensive effects, the acute oral database is considered inadequate for derivation of an acute-duration oral MRL.

Agency Contacts (Chemical Managers): Carolyn Harper

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,1,1-Trichloroethane
CAS Numbers: 71-55-6
Date: March 2024
Profile Status: Final
Route: Oral
Duration: Intermediate
MRL: 2 mg/kg/day
Critical Effect: Reduction in body weight gain
Reference: NTP 2000
Point of Departure: $BMDL_{10}$ of 208 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 14
Species: Mouse

***MRL Summary*:** An intermediate-duration oral MRL of 2 mg/kg/day was derived for 1,1,1-trichloroethane based on a decrease in body weight gain in mice given diets containing encapsulated 1,1,1-trichloroethane (NTP 2000). The MRL is based on a $BMDL_{10}$ of 208 mg/kg/day divided by a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

***Selection of the Critical Effect*:** A number of studies have evaluated the toxicity of 1,1,1-trichloroethane following intermediate-duration oral exposure; the potential endpoints examined include kidney and liver effects (Bruckner et al. 2001; NTP 2000), developmental and reproductive effects (Dow Chemical 1993; George et al. 1989; Lane et al. 1982; NTP 1988a, 1988b, 2000), and body weight effects (Bruckner et al. 2001; George et al. 1989; NTP 2000). The LOAELs for these studies range from 500 to 4,800 mg/kg/day. Table A-4 has a summary of relevant effect levels.

Table A-4. Summary of Relevant NOAEL and LOAEL Values Considered for Derivation of an Intermediate-Duration Oral MRL for 1,1,1-Trichloroethane

Species	Duration/ route	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	$BMDL_{10}$[a] (mg/kg/day)	Effect	Reference
Hepatic effects						
Rat Sprague-Dawley	13 weeks 5 days/week (GO)		500		144% increase in SDH activity	Bruckner et al. 2001
Rat F344/N	13 weeks (F)	2,500 F	5,000 F		11% decrease in relative liver weight	NTP 2000
		2,400 M	4,800 M	4,621	12% decrease in relative liver weight	
Renal effects						
Rat F344/N	13 weeks (F)	600 M	1,200 M		7/10 showed chronic inflammation	NTP 2000

Table A-4. Summary of Relevant NOAEL and LOAEL Values Considered for Derivation of an Intermediate-Duration Oral MRL for 1,1,1-Trichloroethane

Species	Duration/ route	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	$BMDL_{10}$[a] (mg/kg/day)	Effect	Reference
Body weight						
Mouse B6C3F1	13 weeks (F)	1,340 F	2,820 F	380/2,192 (body weight gain/terminal body weight)	22% decrease in body weight gain	NTP 2000
Mouse B6C3F1	13 weeks (F)	1,340 F	850 M	208/678 (body weight gain/terminal body weight)	18% decrease in body weight gain	NTP 2000
Rat F344/N	13 weeks (F)	2,400 M	4,800 M	3,844 (terminal body weight)	10% decrease in final body weight	NTP 2000

[a]BMR is 10% relative deviation.

(F) = food; F = female(s); (GO) = gavage in oil vehicle; LOAEL = lowest-observed-adverse-effect level; M= male(s); NOAEL = no-observed-adverse-effect level; SDH = sorbitol dehydrogenase

The available data suggest that decreases in body weight gain are the most appropriate endpoint following intermediate-duration oral exposure. In female mice, decreased body weight gain was observed at 2,820 mg/kg/day, and in male mice, decreased body weight and body weight gain were observed at 850 mg/kg/day(NTP 2000). Although renal effects were seen at 1,200 mg/kg/day, chronic renal inflammation is a nonspecific effect, and hyaline degeneration in renal tubules occurred at 100% incidence at the LOAEL, which prevents any reasonable modeling of a dose-response relationship. There were also lower doses administered in the Bruckner et al. (2001) study that yielded changes in liver enzymes. Specifically, in Sprague-Dawley rats, increased SDH enzyme activity was observed following intermediate-duration exposure to 500 mg/kg/day via gavage. However, it may not be appropriate, in this case, to base an MRL on an effect level from a gavage study due to toxicokinetic considerations (e.g., possible bolus saturation of the detoxification/excretion mechanism). No other intermediate-duration oral study exhibited the hepatic effects observed in Bruckner et al. (2001).

Selection of the Principal Study: NTP (2000) conducted a study on effects of 1,1,1-trichloroethane oral exposure in rats and mice. There was a dose-related decrease in final mean body weight gain in male B6C3F1 mice at 5,000 ppm; mean body weight gain progressively decreased from 11.2 g at 5,000 ppm to 8.7 g at 80,000 ppm.

Summary of the Principal Study:

NTP. 2000. Technical report on the toxicity studies of 1,1,1-trichloroethane (CAS No. 71-55-6) administered in microcapsules in feed to F344/N rats and B6C3F1 mice. National Toxicology Program. (41) NIH 004402.

Groups of male and female B6C3F1 mice (10 per group) were fed diets containing 0 (untreated feed); 0 (microcapsule vehicle in feed); 5,000, 10,000, 20,000, 40,000, or 80,000 ppm of microencapsulated 1,1,1-trichloroethane (99% pure) 7 days/week for 13 weeks. Average daily doses calculated by the researchers were 850, 1,750, 3,500, 7,370, and 15,000 mg/kg in male mice and 1,340, 2,820, 5,600,

11,125, and 23,000 mg/kg in female mice. Clinical signs and body weights were recorded weekly. Food consumption was determined every 3–4 days. Water consumption was not reported. Vaginal cytology and sperm motility evaluations were performed on all mice in the vehicle control and the three highest dose groups of mice. At necropsy, all mice were subjected to gross pathological examinations, and the heart, lungs, thymus, liver, right kidney, and right testis were weighed. Mice in untreated and vehicle control and high-dose groups were subjected to complete histopathologic examinations.

There were no exposure-related deaths and no indications of treatment-related or histopathological effects. Food consumption was slightly increased in 1,1,1-trichloroethane-treated groups, relative to untreated and vehicle controls. However, final mean body weight and mean body weight gain of all treatment groups of male and female mice were lower than those of respective vehicle controls (see Table A-5). The final mean body weights in the 5,000, 10,000, 20,000, 40,000, and 80,000 ppm groups were 91, 91, 88, 90, and 85% (males) and 97, 93, 89, 88, and 84% (females) of the respective vehicle control means. As demonstrated in Table A-5, the treatment-related effects on final mean body weight and body weight gain reached the level of statistical significance in all treated groups of male mice and ≥20,000-ppm female mice, relative to vehicle controls. The 10,000-ppm group of female mice exhibited a significantly lower mean body weight gain, but not final mean body weight, relative to vehicle controls. NTP (2000) estimated the dose of 10,000 ppm (1,750 and 2,820 mg/kg/day in male and female mice, respectively) to represent a NOAEL. According to ATSDR policy, a treatment-related change in body weight ≥10% (relative to controls) may be considered to represent an adverse effect. Therefore, the 20,000 ppm (3,500 and 5,600 mg/kg/day in males and females, respectively) level is considered to represent a LOAEL for decreased mean terminal body weight (≥10% lower than control values).

Table A-5. Body Weight Data for Mice Administered 1,1,1-Trichloroethane in the Diet for 13 Weeks

Dose (mg/kg/day)	Final mean body weight (g) (±SE)	Percent of control[a] (final body weight)	Mean weight gain (g) (±SE)	Percent of control[a] (body weight gain)
Males				
Vehicle control	36.9±0.7		13.7±0.5	
850	33.6±0.7[b]	91	11.2±0.5[b]	82
1,750	33.7±0.6[b]	91	10.8±0.5[b]	79
3,500	32.7±0.5[b]	88	9.9±0.4[b]	72
7,370	33.1±0.5[b]	90	10.0±0.3[b]	73
15,000	31.3±0.4[b]	85	8.7±0.3[b]	64
Females				
Vehicle control	29.3±0.8		11.2±0.8	
1,340	28.4±0.6	97	9.6±0.7	86
2,820	27.2±0.8	93	8.7±0.6[b]	78
5,600	26.0±0.8[b]	89	7.5±0.7[b]	67
11,125	25.8±0.7[b]	88	7.2±0.6[b]	64
23,000	24.5±0.5[b]	84	6.2±0.5[b]	55

[a]Percent decrease relative to vehicle control.
[b]Significantly different (p≤0.01) from the vehicle control group.

SE = standard error

Source: NTP 2000

***Selection of the Point of Departure for the MRL*:** BMD modeling was conducted to identify a point of departure (POD) using the body weight gain data in male mice given diets containing encapsulated 1,1,1-trichloroethane. Male mean body weight gain data from B6C3F1 mice, using the vehicle control as the control group, were selected for BMD analysis (Table A-5). This analysis used only terminal bodyweight of the male mice whereas the MRL previously derived for this duration of exposure was based on the terminal body weight of male and female mice in the study. The data were fit to all available continuous models in EPA's Benchmark Dose Software (BMDS, version 3.2) using a benchmark response (BMR) of 10% relative deviation from the vehicle control, as this change in body weight is the minimal level of change generally considered to be biologically significant, according to the EPA BMD guidance (EPA 2012). Default setting for the application of restrictions were used. Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, BMDL <10 times the lowest non-zero dose, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all models providing adequate fit to the data, the BMDL from the model with the lowest Akaike's Information Criterion (AIC) was chosen, since all BMDLs from the viable estimated models were within a 3-fold range. BMDS recommended the frequentist restricted Hill model with constant variance for body weight gain, and after verifying the model fit by the four criteria listed above, this model was selected as the basis for estimating this MRL. The only viable model output was this frequentist restricted Hill model, and as such, the BMD/BMDL values for MRL derivation are presented in Table A-6 and the fit of the selected model is presented in Figure A-1.

Table A-6. Selected Results from BMD Analysis of Body Weight Gain in Male Mice Given Diets Containing Encapsulated 1,1,1-Trichloroethane 7 Days/Week for 13 Weeks at Concentrations Resulting in Estimated Doses of 0 (Vehicle Controls), 850, 1,750, 3,500, 7,300, or 15,000 mg/kg/day (NTP 2000)

					Scaled residual[b]	
Model	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)	p-Value[a]	AIC	Dose above BMD	Dose below BMD
Exponential 2 (CV, normal)	4,258.10	3,267.94	<0.0001	230.72	-2.13	3.51
Exponential 3 (CV, normal)	4,258.06	3,267.95	<0.0001	230.72	-2.13	3.51
Exponential 4 (CV, normal)	529.27	304.03	0.09	214.29	-0.97	0.31
Exponential 5 (CV, normal)	527.41	304.03	0.09	214.29	-0.96	0.31
Hill (CV, normal)	**401.75**	**207.93**	**0.29**	**211.54**	**0.12**	**0.12**
Polynomial Degree 5 (CV, normal)	5,014.06	4,447.11	<0.0001	232.31	-2.20	3.69
Polynomial Degree 4 (CV, normal)	5,014.06	4,010.10	<0.0001	232.31	-2.20	3.69
Polynomial Degree 3 (CV,- normal)	5,014.06	4,010.14	<0.0001	232.31	-2.20	3.69
Polynomial Degree 2 (CV, normal)	5,014.06	4,010.18	<0.0001	232.31	-2.20	3.69

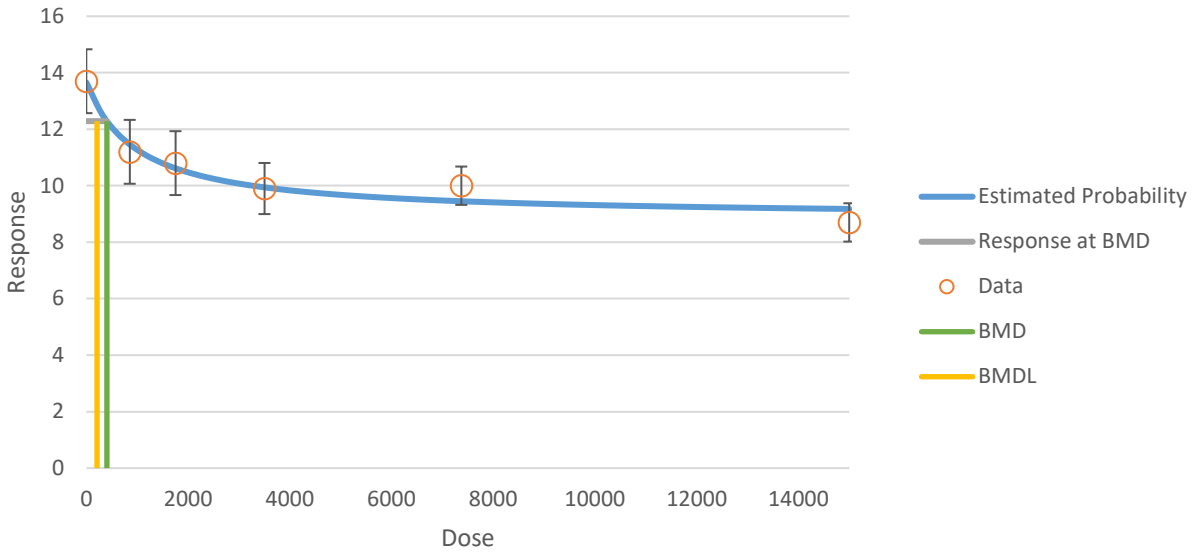
Table A-6. Selected Results from BMD Analysis of Body Weight Gain in Male Mice Given Diets Containing Encapsulated 1,1,1-Trichloroethane 7 Days/Week for 13 Weeks at Concentrations Resulting in Estimated Doses of 0 (Vehicle Controls), 850, 1,750, 3,500, 7,300, or 15,000 mg/kg/day (NTP 2000)

					Scaled residual[b]	
Model	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)	p-Value[a]	AIC	Dose above BMD	Dose below BMD
Power (CV, normal)	5,014.05	4,010.59	<0.0001	232.31	-2.20	3.69
Linear (CV, normal)	5,014.06	4,010.56	<0.0001	232.31	-2.20	3.69

[a]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.

AIC = Akaike Information Criterion; BMD = benchmark dose (maximum likelihood estimate of the dose associated with the selected benchmark response); $BMDL_{10}$ = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., 10 = dose associated with 10% relative deviation from control); CV = constant variance

Figure A-1. Fit of Hill Model to Data on Mean Body Weight Gain (in g) in Male Mice Given Diets Containing Encapsulated 1,1,1-Trichloroethane 7 Days/Week for 13 Weeks at Concentrations Resulting in Estimated Doses of 0 (Vehicle Controls), 850, 1,750, 3,500, 7,300, or 15,000 mg/kg/day



Uncertainty Factor: The $BMDL_{10}$ of 208 mg/kg/day was divided by a total uncertainty factor of 100 (10 for human variability and 10 for extrapolation from animals to humans), resulting in an MRL of 2 mg/kg/day.

- 10 for extrapolation from animals to humans
- 10 for human variability

$MRL = BMDL_{10} \div$ uncertainty factors
$208 \text{ mg/kg/day} \div (10 \times 10) = 2.08 \text{ mg/kg/day} \approx 2 \text{ mg/kg/day}$

Other Additional Studies or Pertinent Information: Decreased body weight appears to be a sensitive effect in other intermediate- and chronic-duration studies by oral or inhalation routes of exposure, either in the absence of other signs of toxicity (Adams et al. 1950; Bruckner et al. 2001; Prendergast et al. 1967) or at doses causing minimal liver lesions (Calhoun et al. 1981; Quast et al. 1988).

Agency Contacts (Chemical Managers): Carolyn Harper, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,1,1-Trichloroethane
CAS Numbers: 71-55-6
Date: March 2024
Profile Status: Final
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration oral MRL due to lack of comprehensive toxicity evaluations.

Rationale for not deriving an MRL: An MRL has not been derived for chronic-duration oral exposure to 1,1,1-trichloroethane. The only noncancer effect following chronic-duration oral exposure to 1,1,1-trichloroethane was decreased body weight observed in two gavage studies (Maltoni et al. 1986; NCI 1977). Maltoni et al. (1986) identified a LOAEL of 500 mg/kg/day (only dose tested) for a 12% decrease in terminal body weight in female rats relative to control. At this same dose, leukemia was also observed. It is likely that decreased terminal body weight was secondary to leukemia rather than a primary effect of 1,1,1-trichloroethane on body weight. This uncertainty precludes body weight effect to derive the MRL. NCI (1977) reported an 18% decrease terminal body weight at 2,807 mg/kg/day (lowest dose tested) in male and female mice. In this study, 22/50 females died and 28/50 males died at the 2,807 mg/kg/day dose. Therefore, a LOAEL of 2,807 mg/kg/day cannot be used to derive a chronic-duration oral MRL.

Agency Contacts (Chemical Managers): Carolyn Harper, Ph.D.

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR 1,1,1-TRICHLOROETHANE

The objective of the toxicological profile is to evaluate the potential for human exposure and the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to 1,1,1-trichloroethane.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen were conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for 1,1,1-trichloroethane. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Foreign language studies are reviewed based on available English-language abstracts and/or tables (or summaries in regulatory assessments, such as International Agency for Research on Cancer [IARC] documents). If the study appears critical for hazard identification or MRL derivation, translation into English is requested. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of 1,1,1-trichloroethane have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of 1,1,1-trichloroethane are presented in Table B-1.

Table B-1. Inclusion Criteria for the Literature Search and Screen

Health Effects
Species
Human
Laboratory mammals
Route of exposure
Inhalation
Oral
Dermal (or ocular)
Parenteral (these studies will be considered supporting data)
Health outcome
Death
Systemic effects
Body weight effects
Respiratory effects
Cardiovascular effects
Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Dermal effects
Ocular effects
Endocrine effects
Immunological effects

Table B-1. Inclusion Criteria for the Literature Search and Screen

Neurological effects
Reproductive effects
Developmental effects
Other noncancer effects
Cancer
Toxicokinetics
Absorption
Distribution
Metabolism
Excretion
PBPK models
Biomarkers
Biomarkers of exposure
Biomarkers of effect
Interactions with other chemicals
Potential for human exposure
Releases to the environment
Air
Water
Soil
Environmental fate
Transport and partitioning
Transformation and degradation
Environmental monitoring
Air
Water
Sediment and soil
Other media
Biomonitoring
General populations
Occupation populations

B.1.1 Literature Search

The current literature search was intended to update the Draft Toxicological Profile for 1,1,1-Trichloroethane released for public comment in 2023; thus, the literature search was restricted to studies published between January 2020 and May 2023. The following main databases were searched in May 2023:

- PubMed
- National Technical Reports Library (NTRL)
- Scientific and Technical Information Network's TOXCENTER

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for 1,1,1-trichloroethane. The query strings used for the literature search are presented in Table B-2.

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance Priority List (SPL) resource page, and other items as needed. Regulations applicable to 1,1,1-trichloroethane were identified by searching international and U.S. agency websites and documents.

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

Table B-2. Database Query Strings

Database search date	Query string
PubMed	
05/2023	(71-55-6[rn] OR "1,1,1-trichloroethane"[nm] OR "1,1,1-TCA"[tw] OR "1,1,1-TCE"[tw] OR "1,1,1-Trichloreothane"[tw] OR "1,1,1-Trichlorethan"[tw] OR "1,1,1-Trichlorethane"[tw] OR "1,1,1-Trichloro-Ethane"[tw] OR "1,1,1-Trichloroethane"[tw] OR "Aerothene TT"[tw] OR "alpha-trichloroethane"[tw] OR "Baltana"[tw] OR "Chlorotene"[tw] OR "Chlorothene"[tw] OR "Chlorten"[tw] OR "Cleanite"[tw] OR "Dowclene LS"[tw] OR "Ethana NU"[tw] OR "Ethane, 1,1,1-trichloro-"[tw] OR "F 140a"[tw] OR "Genklene LB"[tw] OR "HCC 140a"[tw] OR "ICI-CF 2"[tw] OR "Inhibisol"[tw] OR "Methyl chloroform"[tw] OR "methyl trichloromethane"[tw] OR "Methylchloroform"[tw] OR "Methyltrichloromethane"[tw] OR "Tafclean"[tw] OR "Three One A"[tw] OR "Three One S"[tw] OR "Tri-ethane"[tw] OR "Trichlorethane"[tw] OR "Trichloro-1,1,1-ethane"[tw] OR "Trichloroethane"[tw] OR "Trichloroethane, 1,1,1-"[tw] OR "Trichloromethylmethane"[tw] OR "Tricloroethane"[tw] OR "Triethane"[tw] OR "α-Trichloroethane"[tw]) AND (2020/10/01:3000[mhda] OR 2020/10/01:3000[crdt] OR 2020/10/01:3000[edat] OR 2020:3000[dp])
NTRL	
05/2023	Date limit 2020-2023 Search Titles OR Keywords; "1,1,1-TCA" OR "1,1,1-TCE" OR "1,1,1-Trichloreothane" OR "1,1,1-Trichlorethan" OR "1,1,1-Trichlorethane" OR "1,1,1-Trichloro-Ethane" OR "1,1,1-Trichloroethane" OR "Aerothene TT" OR "alpha-trichloroethane" OR "Baltana" OR "Chlorotene" OR "Chlorothene" OR "Chlorten" OR "Cleanite" OR "Dowclene LS" OR "Ethana NU" OR "Ethane, 1,1,1-trichloro-" OR "F 140a" OR "Genklene LB" OR "HCC 140a" OR "ICI-CF 2" OR "Inhibisol" OR "Methyl chloroform" OR "methyl trichloromethane" OR "Methylchloroform" OR "Methyltrichloromethane" OR "Tafclean" OR "Three One A" OR "Three One S" OR "Tri-ethane" OR "Trichlorethane" OR "Trichloro-1,1,1-ethane" OR "Trichloroethane" OR "Trichloroethane, 1,1,1-" OR "Trichloromethylmethane" OR "Tricloroethane" OR "Triethane" OR "α-Trichloroethane"
Toxcenter	
05/2023	FILE 'TOXCENTER' ENTERED AT 19:48:14 ON 25 MAY 2023 L1 8750 SEA FILE=TOXCENTER 71-55-6 L2 8278 SEA FILE=TOXCENTER L1 NOT TSCATS/FS

Table B-2. Database Query Strings

Database search date	Query string
	L3 7680 SEA FILE=TOXCENTER L2 NOT PATENT/DT L4 220 SEA FILE=TOXCENTER L3 AND ED>=20201001 L5 261 SEA FILE=TOXCENTER L3 AND PY>2019 L6 270 SEA FILE=TOXCENTER L4 OR L5 ACT TOXQUERY/Q --------- L7 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L8 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L9 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L10 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L11 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L12 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L13 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L14 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L15 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L16 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L17 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L18 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L19 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?) L20 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?) L21 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?) L22 QUE (ENDOCRIN? AND DISRUPT?) L23 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?) L24 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?) L25 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?) L26 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?) L27 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?) L28 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?) L29 QUE (NEPHROTOX? OR HEPATOTOX?)

Table B-2. Database Query Strings

Database search date	Query string
	L30 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?) L31 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?) L32 QUE L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 OR L30 OR L31 L33 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?) L34 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE) L35 QUE L32 OR L33 OR L34 L36 QUE (NONHUMAN MAMMALS)/ORGN L37 QUE L35 OR L36 L38 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) L39 QUE L37 OR L38 --------- L40 128 SEA FILE=TOXCENTER L6 AND L39 L41 7 SEA FILE=TOXCENTER L40 AND MEDLINE/FS L42 121 SEA FILE=TOXCENTER L40 NOT MEDLINE/FS L43 126 DUP REM L41 L42 (2 DUPLICATES REMOVED) L*** DEL 7 S L40 AND MEDLINE/FS L*** DEL 7 S L40 AND MEDLINE/FS L44 7 SEA FILE=TOXCENTER L43 L*** DEL 121 S L40 NOT MEDLINE/FS L*** DEL 121 S L40 NOT MEDLINE/FS L45 119 SEA FILE=TOXCENTER L43 L46 119 SEA FILE=TOXCENTER (L44 OR L45) NOT MEDLINE/FS D SCAN L46

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
05/2023	Compounds searched: 71-55-6
NTP	
05/2023	"71-55-6" "1,1,1-Trichloroethane" "Trichloroethane" "Trichloromethylmethane" "1,1,1-TCA" "1,1,1-TCE" "1,1,1-Trichloro-Ethane" "Chlorothene" "Methylchloroform" "Tricloroethane" "Methyl chloroform" "Ethane, 1,1,1-trichloro-"

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
Regulations.gov	
05/2023	Docket search (not date limited) Notice search (limited to posted date 2020 to 2023-05-25) "71-55-6" Trichloroethane Chlorothene "Methyl chloroform" Methylchloroform Trichloromethylmethane Trichlorethane
NIH RePORTER	
09/2023	Fiscal Year: Active Projects Text Search (advanced): "1,1,1-TCA" OR "1,1,1-TCE" OR "1,1,1-Trichloreothane" OR "1,1,1-Trichlorethan" OR "1,1,1-Trichlorethane" OR "1,1,1-Trichloro-Ethane" OR "1,1,1-Trichloroethane" OR "Aerothene TT" OR "alpha-trichloroethane" OR "Baltana" OR "Chlorotene" OR "Chlorothene" OR "Chlorten" OR "Cleanite" OR "Dowclene LS" OR "Ethana NU" OR "Ethane, 1,1,1-trichloro-" OR "F 140a" OR "Genklene LB" OR "HCC 140a" OR "ICI-CF 2" OR "Inhibisol" OR "Methyl chloroform" OR "methyl trichloromethane" OR "Methylchloroform" OR "Methyltrichloromethane" OR "Tafclean" OR "Three One A" OR "Three One S" OR "Tri-ethane" OR "Trichlorethane" OR "Trichloro-1,1,1-ethane" OR "Trichloroethane" OR "Trichloroethane, 1,1,1-" OR "Trichloromethylmethane" OR "Tricloroethane" OR "Triethane" OR "α-Trichloroethane" Limit to: Project Title, Project Terms, Project Abstracts
Other	Identified throughout the assessment process

The 2023 results were:

- Number of records identified from PubMed, NTRL, and TOXCENTER (after duplicate removal): 211
- Number of records identified from other strategies: 82
- Total number of records to undergo literature screening: 293

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on 1,1,1-trichloro-ethane:

- Title and abstract screen
- Full text screen

Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

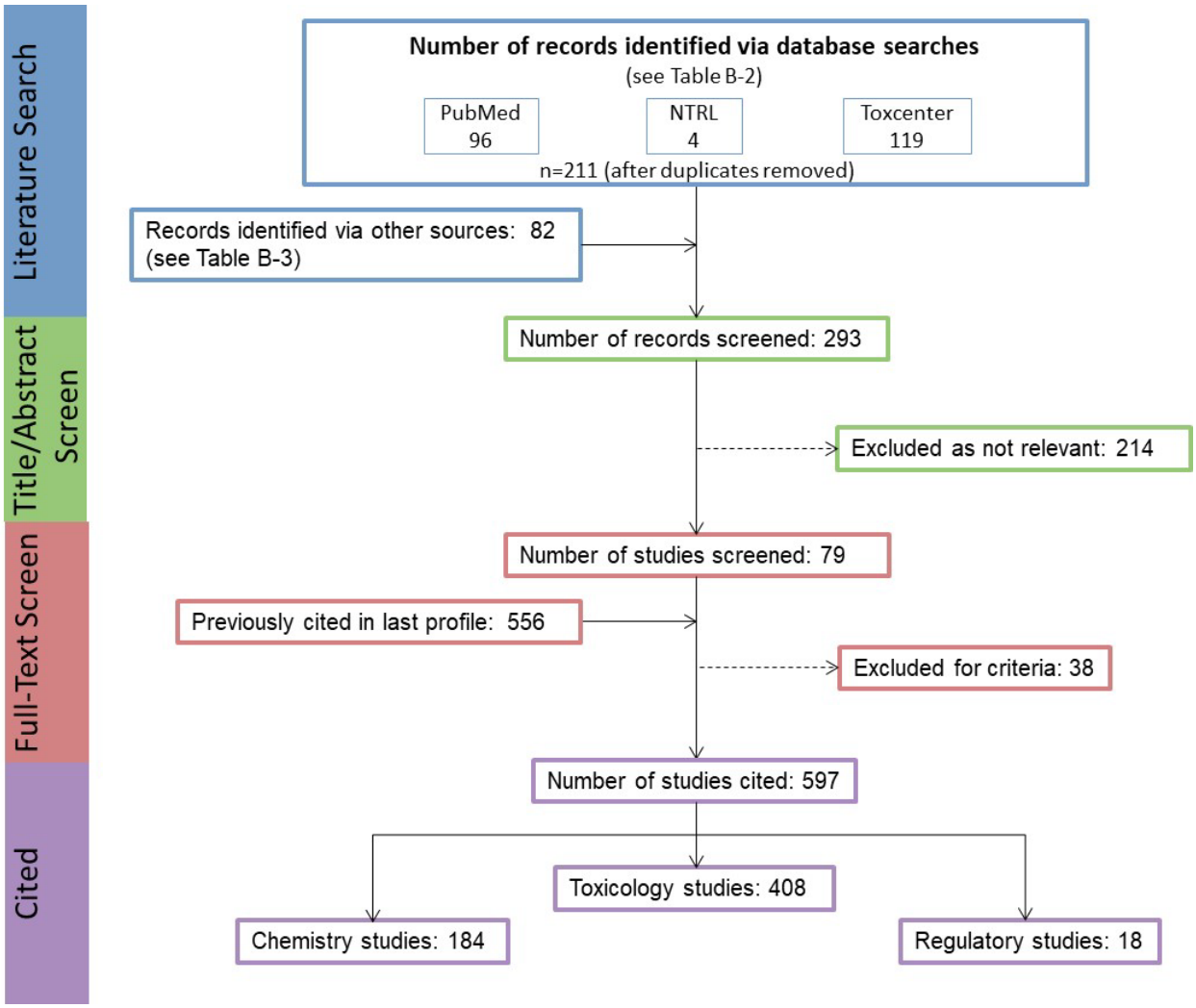
- Number of titles and abstracts screened: 293
- Number of studies considered relevant and moved to the next step: 79

Full Text Screen. The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile.

- Number of studies undergoing full text review: 79
- Number of studies cited in the pre-public draft of the toxicological profile: 556
- Total number of studies cited in the profile: 597

A summary of the results of the literature search and screening is presented in Figure B-1.

Figure B-1. May 2023 Literature Search Results and Screen for 1,1,1-Trichloroethane



APPENDIX C. FRAMEWORK FOR ATSDR'S SYSTEMATIC REVIEW OF HEALTH EFFECTS DATA FOR 1,1,1-TRICHLOROETHANE

To increase the transparency of ATSDR's process of identifying, evaluating, synthesizing, and interpreting the scientific evidence on the health effects associated with exposure to 1,1,1-trichloroethane, ATSDR utilized a slight modification of NTP's Office of Health Assessment and Translation (OHAT) systematic review methodology (NTP 2013, 2015; Rooney et al. 2014). ATSDR's framework is an eight-step process for systematic review with the goal of identifying the potential health hazards of exposure to 1,1,1-trichloroethane:

- Step 1. Problem Formulation
- Step 2. Literature Search and Screen for Health Effects Studies
- Step 3. Extract Data from Health Effects Studies
- Step 4. Identify Potential Health Effect Outcomes of Concern
- Step 5. Assess the Risk of Bias for Individual Studies
- Step 6. Rate the Confidence in the Body of Evidence for Each Relevant Outcome
- Step 7. Translate Confidence Rating into Level of Evidence of Health Effects
- Step 8. Integrate Evidence to Develop Hazard Identification Conclusions

C.1 PROBLEM FORMULATION

The objective of the toxicological profile and this systematic review was to identify the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to 1,1,1-trichloroethane. The inclusion criteria used to identify relevant studies examining the health effects of 1,1,1-trichloroethane are presented in Table C-1.

Data from human and laboratory animal studies were considered relevant for addressing this objective. Human studies were divided into two broad categories: observational epidemiology studies and controlled exposure studies. The observational epidemiology studies were further divided: cohort studies (retrospective and prospective studies), population studies (with individual data or aggregate data), and case-control studies.

Table C-1. Inclusion Criteria for Identifying Health Effects Studies

Species
Human
Laboratory mammals
Route of exposure
Inhalation
Oral
Dermal (or ocular)
Parenteral (these studies will be considered supporting data)
Health outcome
Death
Systemic effects
Body weight effects
Respiratory effects

Table C-1. Inclusion Criteria for Identifying Health Effects Studies

Cardiovascular effects
Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Dermal effects
Ocular effects
Endocrine effects
Immunological effects
Neurological effects
Reproductive effects
Developmental effects
Other noncancer effects
Cancer

C.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

A literature search and screen were conducted to identify studies examining the health effects of 1,1,1-trichloroethane. The literature search framework for the toxicological profile is discussed in detail in Appendix B.

C.2.1 Literature Search

As noted in Appendix B, the current literature search was intended to update the Draft Toxicological Profile for 1,1,1-Trichloroethane released for public comment in 2023. See Appendix B for the databases searched and the search strategy.

A total of 293 records relevant to all sections of the toxicological profile were identified (after duplicate removal).

C.2.2 Literature Screening

As described in Appendix B, a two-step process was used to screen the literature search to identify relevant studies examining the health effects of 1,1,1-trichloroethane.

Title and Abstract Screen. In the Title and Abstract Screen step, 293 records were reviewed; no new documents were considered to meet the health effects inclusion criteria in Table C-1 and were moved to the next step in the process.

Full Text Screen. In the second step in the literature screening process for the systematic review, a full text review of 144 health effect documents (documents cited in older versions of the profile) was performed.

C.3 EXTRACT DATA FROM HEALTH EFFECTS STUDIES

Relevant data extracted from the individual studies selected for inclusion in the systematic review were collected in customized data forms. A summary of the type of data extracted from each study is presented in Table C-2. For references that included more than one experiment or species, data extraction records were created for each experiment or species.

Table C-2. Data Extracted From Individual Studies

Citation
Chemical form
Route of exposure (e.g., inhalation, oral, dermal)
Specific route (e.g., gavage in oil, drinking water)
Species
Strain
Exposure duration category (e.g., acute, intermediate, chronic)
Exposure duration
Frequency of exposure (e.g., 6 hours/day, 5 days/week)
Exposure length
Number of animals or subjects per sex per group
Dose/exposure levels
Parameters monitored
Description of the study design and method
Summary of calculations used to estimate doses (if applicable)
Summary of the study results
Reviewer's comments on the study
Outcome summary (one entry for each examined outcome)
No-observed-adverse-effect level (NOAEL) value
Lowest-observed-adverse-effect level (LOAEL) value
Effect observed at the LOAEL value

A summary of the extracted data for each study is presented in the Supplemental Document for 1,1,1-Trichloroethane and overviews of the results of the inhalation, oral, and dermal exposure studies are presented in Sections 2.2–2.18 of the profile and in the Levels Significant Exposures tables in Section 2.1 of the profile.

C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

Overviews of the potential health effect outcomes for 1,1,1-trichloroethane identified in human and animal studies are presented in Tables C-3 and C-4, respectively. The human studies assessed for the systematic review examined a limited number of endpoints and reported neurological, respiratory, cardiovascular, dermal, reproductive, and developmental effects. Case studies were not included in the systematic review. Animal studies examined a comprehensive set of endpoints following inhalation, oral, or dermal exposure. Evaluation of the literature indicated the most sensitive endpoints associated with 1,1,1-trichloroethane exposure include neurological and hepatic endpoints as effects were observed at low doses, and are supported by common reports of these effects in case studies. Studies examining these potential outcomes were carried through to Steps 4–8 of the systematic review.

APPENDIX C

Table C-3. Overview of the Health Outcomes for 1,1,1-Trichloroethane Evaluated In Human Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological	Neurological	Reproductive	Developmental	Other Noncancer	Caner
Inhalation studies																	
Cohort		3 1	3 1		2 0		6 0	2 0					13 8	1 0			2 1
Case control									2 1					3 0			12 1
Population					1 0								2 0		1 1	1 1	
Case series																	
Oral studies																	
Cohort																	
Case control																	
Population																	
Case series																	
Dermal studies																	
Cohort																	
Case control																	
Population																	
Case series																	

Number of studies examining endpoint	0	1	2	3	4	5–9	≥10
Number of studies reporting outcome	0	1	2	3	4	5–9	≥10

APPENDIX C

Table C-4. Overview of the Health Outcomes for 1,1,1-Trichloroethane Evaluated in Experimental Animal Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological[a]	Neurological[a]	Reproductive[a]	Developmental	Other Noncancer	Caner
Inhalation studies																	
Acute-duration	8	2	2		1		9	2	1	3	1	1	31	3	4		
	2	0	1		0		1	1	1	2	0	0	21	1	2		
Intermediate-duration	30	26	19	3	16	1	32	29	1	1		21	9	14	1		
	12	2	0	0	0	0	4	0	0	0		0	2	2	1		
Chronic-duration	4	3	2	2	4	2	3	4	1	1		3	4	2	1		2
	0	0	0	0	0	0	2	1	0	1		0	1	0	0		0
Acute-duration	4						5	1					2				
	0						1	0					2				
Intermediate-duration	4	1	1				2	2					1	6	6		
	3	1	0				2	0					1	0	1		
Chronic-duration	2	22	2	2	2	2	2	2	2			2	2	2	1		1
	1	0	0	0	0	0	0	0	0			0	0	0	0		1
Dermal studies																	
Acute-duration																	
Intermediate-duration	1	1	1	1	1	1	1	1	1	1	1	1	1	1		1	
	0	0	1	1	0	0	0	0	1	0	0	1	0	0		0	
Chronic-duration																	

Number of studies examining endpoint	0	1	2	3	4	5–9	≥10	
Number of studies reporting outcome	0	1	2	3	4	5–9	≥10	

[a]Number of studies examining endpoint includes study evaluating histopathology, but not evaluating function.

C.5 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES

C.5.1 Risk of Bias Assessment

The risk of bias of individual studies was assessed using OHAT's Risk of Bias Tool (NTP 2015). The risk of bias questions for observational epidemiology studies, human-controlled exposure studies, and animal experimental studies are presented in Tables C-5, C-6, and C-7, respectively. Each risk of bias question was answered on a four-point scale:

- **Definitely low risk of bias (++)**
- **Probably low risk of bias (+)**
- **Probably high risk of bias (-)**
- **Definitely high risk of bias (– –)**

In general, "definitely low risk of bias" or "definitely high risk of bias" were used if the question could be answered with information explicitly stated in the study report. If the response to the question could be inferred, then "probably low risk of bias" or "probably high risk of bias" responses were typically used.

Table C-5. Risk of Bias Questionnaire for Observational Epidemiology Studies

Selection bias
Were the comparison groups appropriate?
Confounding bias
Did the study design or analysis account for important confounding and modifying variables?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

Table C-6. Risk of Bias Questionnaire for Human-Controlled Exposure Studies

Selection bias
Was administered dose or exposure level adequately randomized?
Was the allocation to study groups adequately concealed?
Performance bias
Were the research personnel and human subjects blinded to the study group during the study?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

Table C-7. Risk of Bias Questionnaire for Experimental Animal Studies

Selection bias
Was administered dose or exposure level adequately randomized?
Was the allocation to study groups adequately concealed?
Performance bias
Were experimental conditions identical across study groups?
Were the research personnel blinded to the study group during the study?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

After the risk of bias questionnaires were completed for the health effects studies, the studies were assigned to one of three risk of bias tiers based on the responses to the key questions listed below and the responses to the remaining questions.

- Is there confidence in the exposure characterization? (only relevant for observational studies)
- Is there confidence in the outcome assessment?
- Does the study design or analysis account for important confounding and modifying variables? (only relevant for observational studies)

First Tier. Studies placed in the first tier received ratings of "definitely low" or "probably low" risk of bias on the key questions **AND** received a rating of "definitely low" or "probably low" risk of bias on the responses to at least 50% of the other applicable questions.

Second Tier. A study was placed in the second tier if it did not meet the criteria for the first or third tiers.

Third Tier. Studies placed in the third tier received ratings of "definitely high" or "probably high" risk of bias for the key questions **AND** received a rating of "definitely high" or "probably high" risk of bias on the response to at least 50% of the other applicable questions.

The results of the risk of bias assessment for the different types of 1,1,1-trichloroethane health effects studies (observational epidemiology, human exposure, and animal experimental studies) are presented in Tables C-8, C-9, and C-10, respectively.

Table C-8. Summary of Risk of Bias Assessment for 1,1,1-Trichloroethane—Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings: Selection bias — Were the comparison groups appropriate?	Confounding bias — Did the study design or analysis account for important confounding and modifying variables?*	Attrition / exclusion bias — Were outcome data complete without attrition or exclusion from analysis?	Detection bias — Is there confidence in the exposure characterization?*	Detection bias — Is there confidence in the outcome assessment?*	Selective reporting bias — Were all measured outcomes reported?	Risk of bias tier
Outcome: Hepatic effects							
Cohort studies, inhalation							
Kramer et al. 1978	+	+	–	+	+	+	First
Kelafant et al. 1994	+	+	+	–	+	+	First
Outcome: Neurological effects							
Cohort studies, inhalation							
Kelafant et al. 1994	+	+	+	–	+	+	First
Maroni et al. 1977	+	–	+	–	+	+	First
Population studies, inhalation							

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; na = not applicable

*Key question used to assign risk of bias tier

Table C-9. Summary of Risk of Bias Assessment for 1,1,1-Trichloroethane—Controlled Exposure Studies

Reference	Risk of bias criteria and ratings							
	Selection bias		Performance Bias	Attrition / exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?*	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	Risk of bias tier
Outcome: Hepatic effects								
Inhalation acute-duration exposure								
Stewart et al. 1961	–	–	–	+	++	+	+	First
Stewart et al. 1969	–	–	–	+	–	+	+	Second
Outcome: Neurological effects								
Inhalation acute-duration exposure								
Gamberale and Hultengren 1973	++	–	–	++	–	++	++	First
Laine et al. 1996	–	–	–	+	+	+	+	First
Stewart et al. 1969	–	–	–	+	–	+	+	Second
Muttray et al. 2000	+	+	-	–	+	+	–	First
Savolainen et al. 1981	–	–	–	++	–	+	+	Second
Stewart et al. 1961	–	–	–	+	++	+	+	First
Salvini et al. 1971	–	–	–	++	–	+	+	Second
Torkelson et al. 1958	–	–	–	+	+	–	–	Second
Mackay et al. 1987	–	–	–	+	–	+	+	Second

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; na = not applicable

*Key question used to assign risk of bias tier

Table C-10. Summary of Risk of Bias Assessment for 1,1,1-Trichloroethane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	Risk of bias tier
Outcome: Hepatic									
Inhalation acute-duration exposure									
Adams et al. 1950 (rat)	–	–	+	–	+	++	+	+	First
Cornish and Adefuin 1966 (rat)	–	–	+	–	+	++	+	+	First
Cornish and Adefuin 1966 (rat)	–	–	+	–	+	++	+	+	First
Herd et al. 1974 (dog)	–	–	+	–	+	++	+	+	First
Koizumi et al. 1983 (rat)	–	–	+	–	+	++	+	+	First
Lal and Shah 1970 (mouse)	–	–	+	–	–	+	+	+	Second
McNutt et al. 1975 (mouse)	+	–	+	–	+	++	+	+	First
Inhalation intermediate-duration exposure									
Adams et al. 1950 (guinea pig)	–	–	+	–	+	++	+	+	First
Adams et al. 1950 (guinea pig)	–	–	+	–	+	++	+	+	First
Adams et al. 1950 (guinea pig)	–	–	+	–	+	++	+	+	First
Adams et al. 1950 (guinea pig)	–	–	+	–	+	++	+	+	First
Adams et al. 1950 (guinea pig)	–	–	+	–	+	++	+	+	First
Adams et al. 1950 (rat)	–	–	+	–	+	++	+	+	First
Adams et al. 1950 (rat)	–	–	+	–	+	++	+	+	First
Adams et al. 1950 (rat)	–	–	+	–	+	++	+	+	First
Adams et al. 1950 (monkey)	–	–	+	–	+	++	+	+	First

Table C-10. Summary of Risk of Bias Assessment for 1,1,1-Trichloroethane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	Risk of bias tier
Calhoun et al. 1981 (rat)	++	–	+	–	+	++	+	+	First
Calhoun et al. 1981 (mouse)	++	–	+	–	+	++	+	+	First
NTP 2000 (rat)	–	–	++	–	++	++	++	++	First
NTP 2000 (mouse)	–	–	++	–	++	++	++	++	First
Toftgard et al. 1981 (rat)	–	–	+	–	+	+	+	+	First
Torkelson et al. 1958 (monkey)	–	–	+	–	+	++	++	++	First
Torkelson et al. 1958 (rat)	–	–	+	–	+	++	++	++	First
Torkelson et al. 1958 (rat)	–	–	+	–	+	++	++	++	First
Torkelson et al. 1958 (guinea pig)	–	–	+	–	+	++	++	++	First
Torkelson et al. 1958 (guinea pig)	–	–	+	–	+	++	++	++	First
Truffert et al. 1977 (rat)	–	–	+	–	+	–	+	+	Second
Inhalation chronic-duration exposure									
NCI 1977 (rat)	–	+	+	–	–	++	+	+	First
NCI 1977 (mouse)	–	+	+	–	–	++	+	+	First
Ohnishi et al. 2013 (rat)	++	–	++	–	+	++	++	++	First
Ohnishi et al. 2013 (mouse)	++	–	++	–	+	++	++	++	First
Oral acute-duration exposure									
Bruckner et al. 2001 (rat)	–	–	++	–	++	++	+	+	First
Bruckner et al. 2001 (rat)	–	–	++	–	++	++	+	+	First

Table C-10. Summary of Risk of Bias Assessment for 1,1,1-Trichloroethane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	Risk of bias tier
Platt and Cockrill 1969 (rat)	–	–	+	–	++	–	+	+	Second
Torkelson et al. 1958 (mouse)	–	–	+	–	+	++	++	++	First
Torkelson et al. 1958 (guinea pig)	–	–	+	–	+	++	++	++	First
Tyson et al. 1983 (rat)	–	–	+	–	+	+	+	+	First
Oral intermediate-duration exposure									
Bruckner et al. 2001 (rat)	–	–	++	–	+	++	+	+	First
Outcome: Neurological									
Inhalation acute-duration exposure									
Bowen et al. 1996a (mouse)	–	–	++	–	++	+	++	++	First
Balster et al. 1982 (mouse)	–	–	++	–	++	+	++	++	First
Bonnet et al. 1980 (rat)	–	–	++	–	++	++	++	++	First
Bowen et al. 1996a (mouse)	–	–	++	–	++	+	++	++	First
Bowen et al. 1996b (mouse)	–	–	++	–	++	+	++	++	First
Bowen and Balster 1998 (mouse)	–	–	++	–	++	+	++	++	First
De Ceaurriz et al. 1981 (mouse)	–	–	++	–	++	+	++	++	First
Folbergrova et al. 1984 (rat)	–	–	++	–	++	+	++	++	First
Geller et al. 1982 (monkey)	–	–	++	–	++	+	++	++	First
Herd et al. 1974 (dog)	–	–	+	–	+	++	+	+	First
Horiguchi and Horiuchi 1971 (mouse)	–	–	–	–	+	–	–	+	Third

Table C-10. Summary of Risk of Bias Assessment for 1,1,1-Trichloroethane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	Risk of bias tier
Hougaard et al. 1984 (rat)	–	–	+	–	++	+	+	+	First
Kjellstrand et al. 1985b (mouse)	–	–	+	–	++	–	++	++	First
Moser and Balster 1986 (mouse)	–	–	++	–	++	+	++	++	First
Moser and Balster 1985 (mouse)	–	–	++	–	+	+	++	++	First
Mullin and Krivanek 1982 (rat)	–	–	++	–	+	++	++	++	First
Nilsson 1986a (mouse)	–	–	++	–	++	+	++	++	First
Nilsson 1986b (mouse)	–	–	++	–	++	+	++	++	First
Paez-Martinez et al. 2003 (mouse)	–	–	++	–	++	++	++	++	First
Woolverton and Balster 1981 (mice)	–	–	++	–	++	+	++	++	First
You and Dallas 2000 (rat)	–	–	++	–	++	++	++	++	First
You and Dallas 2000 (mouse)	–	–	++	–	++	++	++	++	First
Inhalation intermediate-duration exposure									
Mattsson et al. 1993 (Mouse)	–	–	++	–	+	+	++	++	First
Moser and Balster 1985 (mouse)	–	–	++	–	+	+	++	++	First
NTP 2000 (rat)	–	–	++	–	++	++	++	++	First
NTP 2000 (mouse)	–	–	++	–	++	++	++	++	First
Prendergast et al. 1967 (monkey)	–	–	++	–	++	++	++	++	First
Prendergast et al. 1967 (monkey)	–	–	++	–	++	++	++	++	First
Prendergast et al. 1967 (rat)	–	–	++	–	++	++	++	++	First

Table C-10. Summary of Risk of Bias Assessment for 1,1,1-Trichloroethane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	Risk of bias tier
Prendergast et al. 1967 (rat)	–	–	++	–	++	++	++	++	First
Prendergast et al. 1967 (guinea pig)	–	–	++	–	++	++	++	++	First
Prendergast et al. 1967 (guinea pig)	–	–	++	–	++	++	++	++	First
Rosengren et al. 1985 (gerbil)	–	–	++	–	++	+	++	++	First
Torkelson et al. 1958 (monkey)	–	–	+	–	+	++	++	++	First
Torkelson et al. 1958 (rat)	–	–	+	–	+	++	++	++	First
Torkelson et al. 1958 (rat)	–	–	+	–	+	++	++	++	First
Torkelson et al. 1958 (guinea pig)	–	–	+	–	+	++	++	++	First
Torkelson et al. 1958 (guinea pig)	–	–	+	–	+	++	++	++	First
Torkelson et al. 1958 (rabbit)	–	–	+	–	+	++	++	++	First
Inhalation chronic-duration exposure									
NCI 1977 (rat)	–	+	+	–	–	++	+	+	First
NCI 1977 (mouse)	–	+	+	–	–	++	+	+	First
Ohnishi et al. 2013 (rat)	++	–	++	–	+	++	++	++	First
Ohnishi et al. 2013 (mouse)	++	–	++	–	+	++	++	++	First
Quast et al. 1988 (rat)	–	–	++	–	+	++	++	++	First
Oral acute-duration exposure									
Torkelson et al. 1958 (mouse)	–	–	+	–	+	++	++	++	First
Torkelson et al. 1958 (guinea pig)	–	–	+	–	+	++	++	++	First

Table C-10. Summary of Risk of Bias Assessment for 1,1,1-Trichloroethane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	Risk of bias tier
Oral intermediate-duration exposure									
Bruckner et al. 2001 (rat)	–	–	++	–	+	++	+	+	First
Oral chronic-duration exposure									
NCI 1977 (rat)	–	+	+	–	–	++	+	+	First
NCI 1977 (mouse)	–	+	+	–	–	++	+	+	First

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; na = not applicable

*Key question used to assign risk of bias tier

C.6 RATE THE CONFIDENCE IN THE BODY OF EVIDENCE FOR EACH RELEVANT OUTCOME

Confidences in the bodies of human and animal evidence were evaluated independently for each potential outcome. ATSDR did not evaluate the confidence in the body of evidence for carcinogenicity; rather, the Agency defaulted to the cancer weight-of-evidence assessment of other agencies including HHS, EPA, and IARC. The confidence in the body of evidence for an association or no association between exposure to 1,1,1-trichloroethane and a particular outcome was based on the strengths and weaknesses of individual studies. Four descriptors were used to describe the confidence in the body of evidence for effects or when no effect was found:

- **High confidence:** the true effect is highly likely to be reflected in the apparent relationship
- **Moderate confidence:** the true effect may be reflected in the apparent relationship
- **Low confidence:** the true effect may be different from the apparent relationship
- **Very low confidence:** the true effect is highly likely to be different from the apparent relationship

Confidence in the body of evidence for a particular outcome was rated for each type of study: case-control, case series, cohort, population, human-controlled exposure, and experimental animal. In the absence of data to the contrary, data for a particular outcome were collapsed across animal species, routes of exposure, and exposure durations. If species (or strain), route, or exposure duration differences were noted, then the data were treated as separate outcomes.

C.6.1 Initial Confidence Rating

In ATSDR's modification to the OHAT approach, the body of evidence for an association (or no association) between exposure to 1,1,1-trichloroethane and a particular outcome was given an initial confidence rating based on the key features of the individual studies examining that outcome. The presence of these key features of study design was determined for individual studies using four "yes or no" questions, which were customized for epidemiology, human controlled exposure, or experimental animal study designs. Separate questionnaires were completed for each outcome assessed in a study. The key features for observational epidemiology (cohort, population, and case-control) studies, human controlled exposure, and experimental animal studies are presented in Tables C-11, C-12, and C-13, respectively. The initial confidence in the study was determined based on the number of key features present in the study design:

- **High Initial Confidence:** Studies in which the responses to the four questions were "yes".
- **Moderate Initial Confidence:** Studies in which the responses to only three of the questions were "yes".
- **Low Initial Confidence:** Studies in which the responses to only two of the questions were "yes".
- **Very Low Initial Confidence:** Studies in which the response to one or none of the questions was "yes".

Table C-11. Key Features of Study Design for Observational Epidemiology Studies

Exposure was experimentally controlled
Exposure occurred prior to the outcome
Outcome was assessed on individual level rather than at the population level
A comparison group was used

Table C-12. Key Features of Study Design for Human-Controlled Exposure Studies

A comparison group was used or the subjects served as their own control
A sufficient number of subjects were tested
Appropriate methods were used to measure outcomes (i.e., clinically-confirmed outcome versus self-reported)
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

Table C-13. Key Features of Study Design for Experimental Animal Studies

A concurrent control group was used
A sufficient number of animals per group were tested
Appropriate parameters were used to assess a potential adverse effect
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

The presence or absence of the key features and the initial confidence levels for studies examining neurological and hepatic effects observed in the observational epidemiology, human-controlled exposure, and animal experimental studies are presented in Tables C-14, C-15, and C-16, respectively.

Table C-14. Presence of Key Features of Study Design for 1,1,1-Trichloroethane—Observational Epidemiology Studies

	Key features				
Reference	Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	Initial study confidence
Outcome: Hepatic					
Cohort studies Inhalation					
Kramer et al. 1978	No	Yes	Yes	Yes	Moderate
Kelafant et al. 1994	No	Yes	Yes	Yes	Moderate

Table C-14. Presence of Key Features of Study Design for 1,1,1-Trichloroethane—Observational Epidemiology Studies

Reference	Key features: Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	Initial study confidence
Outcome: Neurological					
Cohort studies Inhalation					
Kelafant et al. 1994	No	Yes	Yes	Yes	Moderate
Maroni et al. 1977	No	No	Yes	Yes	Low

Table C-15. Presence of Key Features of Study Design for 1,1,1-Trichloroethane—Human-Controlled Exposure Studies

Reference	Key features: Comparison group or aerved as own controls	Sufficient number of subjects tested	Appropriate outcome assessment	Appropriate statistical analysis	Initial study confidence
Outcome: Hepatic effects					
Inhalation acute-duration exposure					
Stewart et al. 1961	Yes	Yes	Yes	No	Moderate
Stewart et al. 1969	No	Yes	Yes	No	Low
Outcome: Neurological effects					
Inhalation acute-duration exposure					
Gamberale and Hultengren 1973	Yes	Yes	Yes	Yes	High
Laine et al. 1996	Yes	Yes	Yes	Yes	High
Stewart et al. 1969	No	Yes	Yes	No	Low
Muttray et al. 2000	Yes	Yes	Yes	Yes	High
Savolainen et al. 1981	Yes	Yes	Yes	Yes	High
Stewart et al. 1961	Yes	Yes	Yes	No	Moderate
Salvini et al. 1971	Yes	Yes	Yes	Yes	High
Torkelson et al. 1958	No	No	Yes	No	Low
Mackay et al. 1987	Yes	Yes	Yes	Yes	High

Table C-16. Presence of Key Features of Study Design for 1,1,1-Trichloroethane— Experimental Animal Studies

Reference	Key features				Initial study confidence
	Controlled Exposure	Exposure prior to outcome	Outcome assessed on individual level	Comparison group	
Outcome: Hepatic effects					
Inhalation acute-duration exposure					
Adams et al. 1950 (rat)	Yes	No	Yes	Yes	Moderate
Cornish and Adefuin 1966 (rat)	Yes	Yes	Yes	Yes	High
Cornish and Adefuin 1966 (rat)	Yes	Yes	Yes	Yes	High
Herd et al. 1974 (dog)	Yes	Yes	Yes	No	Moderate
Koizumi et al. 1983 (rat)	Yes	Yes	Yes	Yes	High
Lal and Shah 1970 (mouse)	Yes	Yes	Yes	Yes	High
Inhalation intermediate-duration exposure					
Adams et al. 1950 (guinea pig)	Yes	No	Yes	Yes	Moderate
Adams et al. 1950 (guinea pig)	Yes	No	Yes	Yes	Moderate
Adams et al. 1950 (guinea pig)	Yes	No	Yes	Yes	Moderate
Adams et al. 1950 (guinea pig)	Yes	No	Yes	Yes	Moderate
Adams et al. 1950 (guinea pig)	Yes	No	Yes	Yes	Moderate
Adams et al. 1950 (rat)	Yes	No	Yes	Yes	Moderate
Adams et al. 1950 (rat)	Yes	No	Yes	Yes	Moderate
Adams et al. 1950 (rat)	Yes	No	Yes	Yes	Moderate
Adams et al. 1950 (monkey)	No	No	Yes	Yes	Low
Calhoun et al. 1981 (rat)	Yes	Yes	Yes	Yes	High
Calhoun et al. 1981 (mouse)	Yes	Yes	Yes	Yes	High
McNutt et al. 1975 (mouse)	Yes	Yes	Yes	Yes	High
NTP 2000 (rat)	Yes	Yes	Yes	Yes	High
NTP 2000 (mouse)	Yes	Yes	Yes	Yes	High
Toftgard et al. 1981 (rat)	Yes	No	Yes	Yes	Moderate
Torkelson et al. 1958 (monkey)	Yes	No	Yes	Yes	Moderate
Torkelson et al. 1958 (rat)	Yes	No	Yes	Yes	Moderate
Torkelson et al. 1958 (rat)	Yes	No	Yes	Yes	Moderate
Torkelson et al. 1958 (guinea pig)	Yes	No	Yes	Yes	Moderate
Torkelson et al. 1958 (guinea pig)	Yes	No	Yes	Yes	Moderate
Truffert et al. 1977 (rat)	Yes	Yes	Yes	No	Moderate
NCI 1977 (rat)	Yes	Yes	Yes	Yes	High
NCI 1977 (mouse)	Yes	Yes	Yes	Yes	High
Ohnishi et al. 2013 (rat)	Yes	Yes	Yes	Yes	High
Ohnishi et al. 2013 (mouse)	Yes	Yes	Yes	Yes	High

Table C-16. Presence of Key Features of Study Design for 1,1,1-Trichloroethane— Experimental Animal Studies

Reference	Key features				Initial study confidence
	Controlled Exposure	Exposure prior to outcome	Outcome assessed on individual level	Comparison group	
Oral acute-duration exposure	Yes	Yes	Yes	Yes	High
Bruckner et al. 2001 (rat)	Yes	Yes	Yes	Yes	High
Bruckner et al. 2001 (rat)	Yes	Yes	Yes	Yes	High
Platt and Cockrill 1969 (rat)	Yes	No	Yes	No	Low
Torkelson et al. 1958 (mouse)	No	Yes	Yes	Yes	Moderate
Torkelson et al. 1958 (guinea pig)	No	Yes	Yes	Yes	Moderate
Tyson et al. 1983 (rat)	Yes	No	Yes	No	Low
Oral intermediate-duration exposure					
Bruckner et al. 2001 (rat)	Yes	Yes	Yes	Yes	High
Oral chronic exposure					
NCI 1977 (rat)	Yes	Yes	Yes	Yes	High
NCI 1977 (mouse)	Yes	Yes	Yes	Yes	High
Outcome: Neurological effects					
Inhalation acute-duration exposure					
Balster et al. 1982 (mouse)	Yes	Yes	Yes	Yes	High
Bonnet et al. 1980 (rat)	Yes	Yes	Yes	Yes	High
Bowen et al. 1996a (mouse)	Yes	Yes	Yes	Yes	High
Bowen et al. 1996b (mouse)	Yes	Yes	Yes	Yes	High
Bowen and Balster 1998 (mouse)	Yes	Yes	Yes	Yes	High
De Ceaurriz et al. 1981 (mouse)	Yes	Yes	Yes	No	Moderate
Folbergrova et al. 1984 (rat)	Yes	Yes	Yes	No	Moderate
Geller et al. 1982 (monkey)	Yes	No	Yes	No	Low
Herd et al. 1974 (dog)	Yes	Yes	Yes	No	Moderate
Horiguchi and Horiuchi 1971 (mouse)	No	Yes	Yes	No	Low
Hougaard et al. 1984 (rat)	Yes	Yes	Yes	Yes	High
Kjellstrand et al. 1985b (mouse)	Yes	Yes	Yes	No	Moderate
Moser and Balster 1986 (mouse)	Yes	Yes	Yes	Yes	High
Moser and Balster 1985 (mouse)	Yes	Yes	Yes	Yes	High
Mullin and Krivanek 1982 (rat)	Yes	Yes	Yes	Yes	High
Nilsson 1986a (mouse)	Yes	Yes	Yes	Yes	High
Nilsson 1986b (mouse)	Yes	Yes	Yes	Yes	High
Paez-Martinez et al. 2003 (mouse)	Yes	Yes	Yes	Yes	High
Woolverton and Balster 1981 (mouse)	Yes	Yes	Yes	Yes	High
You and Dallas 2000 (rat)	Yes	Yes	Yes	Yes	High
You and Dallas 2000 (mouse)	Yes	Yes	Yes	Yes	High

Table C-16. Presence of Key Features of Study Design for 1,1,1-Trichloroethane— Experimental Animal Studies

Reference	Key features: Controlled Exposure	Exposure prior to outcome	Outcome assessed on individual level	Comparison group	Initial study confidence
Inhalation intermediate-duration exposure					
Mattsson et al. 1993 (rat)	Yes	Yes	Yes	Yes	High
Moser and Balster 1985 (mouse)	Yes	Yes	Yes	Yes	High
NTP 2000 (rat)	Yes	Yes	Yes	Yes	High
NTP 2000 (mouse)	Yes	Yes	Yes	Yes	High
Prendergast et al. 1967 (monkey)	Yes	Yes	Yes	Yes	High
Prendergast et al. 1967 (monkey)	Yes	Yes	Yes	Yes	High
Prendergast et al. 1967 (rat)	Yes	Yes	Yes	Yes	High
Prendergast et al. 1967 (rat)	Yes	Yes	Yes	Yes	High
Prendergast et al. 1967 (guinea pig)	Yes	Yes	Yes	Yes	High
Prendergast et al. 1967 (guinea pig)	Yes	Yes	Yes	Yes	High
Rosengren et al. 1985 (gerbil)	Yes	Yes	Yes	Yes	High
Torkelson et al. 1958 (monkey)	Yes	No	Yes	Yes	Moderate
Torkelson et al. 1958 (rat)	Yes	No	Yes	Yes	Moderate
Torkelson et al. 1958 (rat)	Yes	No	Yes	Yes	Moderate
Torkelson et al. 1958 (guinea pig)	Yes	No	Yes	Yes	Moderate
Torkelson et al. 1958 (guinea pig)	Yes	No	Yes	Yes	Moderate
Torkelson et al. 1958 (rabbit)	Yes	No	Yes	Yes	Moderate
Truffert et al. 1977 (rat)	Yes	Yes	Yes	No	Moderate
Inhalation chronic-duration exposure					
NCI 1977 (rat)	Yes	Yes	Yes	Yes	High
NCI 1977 (mouse)	Yes	Yes	Yes	Yes	High
Ohnishi et al. 2013 (rat)	Yes	Yes	Yes	Yes	High
Ohnishi et al. 2013 (mouse)	Yes	Yes	Yes	Yes	High
Quast et al. 1988 (rat)	Yes	Yes	Yes	Yes	High
Oral acute-duration exposure					
Torkelson et al. 1958 (mouse)	No	Yes	Yes	Yes	Moderate
Torkelson et al. 1958 (guinea pig)	No	Yes	Yes	Yes	Moderate
Oral intermediate-duration exposure					
Bruckner et al. 2001 (rat)	Yes	Yes	Yes	Yes	High
Oral chronic-duration exposure					
NCI 1977 (rat)	Yes	Yes	Yes	Yes	High
NCI 1977 (mouse)	Yes	Yes	Yes	Yes	High

A summary of the initial confidence ratings for each outcome is presented in Table C-17. If individual studies for a particular outcome and study type had different study quality ratings, then the highest confidence rating for the group of studies was used to determine the initial confidence rating for the body of evidence; any exceptions were noted in Table C-17.

Table C-17. Initial Confidence Rating for 1,1,1-Trichloroethane Health Effects Studies

Reference	Initial study confidence	Initial confidence rating
Outcome: Hepatic effects		
Inhalation acute-duration exposure		
Animal studies		
Adams et al. 1950 (rat)	Moderate	High
Cornish and Adefuin 1966 (rat)	High	
Cornish and Adefuin 1966 (rat)	High	
Herd et al. 1974 (dog)	Moderate	
Koizumi et al. 1983 (rat)	High	
Lal and Shah 1970 (mouse)	High	
Inhalation intermediate-duration exposure		
Adams et al. 1950 (guinea pig)	Moderate	High
Adams et al. 1950 (guinea pig)	Moderate	
Adams et al. 1950 (guinea pig)	Moderate	
Adams et al. 1950 (guinea pig)	Moderate	
Adams et al. 1950 (guinea pig)	Moderate	
Adams et al. 1950 (rat)	Moderate	
Adams et al. 1950 (rat)	Moderate	
Adams et al. 1950 (rat)	Moderate	
Adams et al. 1950 (monkey)	Low	
Calhoun et al. 1981 (rat)	High	
Calhoun et al. 1981 (mouse)	High	
McNutt et al. 1975 (mouse)	High	
NTP 2000 (rat)	High	
NTP 2000mouse)	High	
Toftgard et al. 1981 (rat)	Moderate	
Torkelson et al. 1958 (monkey)	Moderate	
Torkelson et al. 1958 (rat)	Moderate	
Torkelson et al. 1958 (rat)	Moderate	
Torkelson et al. 1958 (guinea pig)	Moderate	
Torkelson et al. 1958 (guinea pig)	Moderate	
Truffert et al. 1977 (rat)	Moderate	
Inhalation chronic-duration exposure		
NCI 1977 (rat)	High	High
NCI 1977 (mouse)	High	
Ohnishi et al. 2013 (rat)	High	
Ohnishi et al. 2013 (mouse)	High	

Table C-17. Initial Confidence Rating for 1,1,1-Trichloroethane Health Effects Studies

Reference	Initial study confidence	Initial confidence rating
Oral acute-duration exposure		
Bruckner et al. 2001 (rat)	High	High
Bruckner et al. 2001 (rat)	High	
Platt and Cockrill 1969 (rat)	High	
Torkelson et al. 1958 (mouse)	Low	
Torkelson et al. 1958 (guinea pig)	Moderate	
Tyson et al. 1983 (rat)	Low	
Oral intermediate-duration exposure		
Bruckner et al. 2001 (rat)	High	High
Oral chronic-duration exposure		
NCI 1977 (rat)	High	High
NCI 1977 (mouse)	High	
Human studies		
Kramer et al. 1978	Moderate	Moderate
Kelafant et al. 1994	Moderate	
Stewart et al. 1961	Moderate	
Stewart et al. 1969	Low	
Outcome: Neurological effects		
Animal studies		
Inhalation acute-duration exposure		
Balster et al. 1982 (mouse)	High	
Bonnet et al. 1980 (Rat)	High	
Bowen et al. 1996a (mouse)	High	
Bowen et al. 1996b (mouse)	High	
Bowen and Balster 1998 (mouse)	High	
De Ceaurriz et al. 1981 (mouse)	Moderate	
Folbergrova et al. 1984 (rat)	Moderate	
Geller et al. 1982 (monkey)	Low	
Herd et al. 1974 (dog)	Moderate	
Horiguchi and Horiuchi 1971 (mouse)	Low	
Hougaard et al. 1984 (rat)	High	
Kjellstrand et al. 1985b (mouse)	Moderate	
Moser and Balster 1986 (mouse)	High	
Moser and Balster 1985 (mouse)	High	
Mullin and Krivanek 1982 (rat)	High	
Nilsson 1986a (mouse)	High	
Nilsson 1986b (mouse)	High	
Paez-Martinez et al. 2003 (mouse)	High	

Table C-17. Initial Confidence Rating for 1,1,1-Trichloroethane Health Effects Studies

Reference	Initial study confidence	Initial confidence rating
Woolverton and Balster 1981 (mouse)	High	
You and Dallas 2000 (rat)	High	
You and Dallas 2000 (mouse)	High	
Inhalation intermediate-duration exposure		
Mattsson et al. 1993 (rat)	High	
Moser and Balster 1985 (mouse)	High	
NTP 2000 (rat)	High	
NTP 2000 (mouse)	High	
Prendergast et al. 1967 (monkey)	High	
Prendergast et al. 1967 (monkey)	High	
Prendergast et al. 1967 (rat)	High	
Prendergast et al. 1967 (rat)	High	
Prendergast et al. 1967 (guinea pig)	High	High
Prendergast et al. 1967 (guinea pig)	High	
Rosengren et al. 1985 (gerbil)	High	
Torkelson et al. 1958 (monkey)	Moderate	
Torkelson et al. 1958 (rat)	Moderate	
Torkelson et al. 1958 (rat)	Moderate	
Torkelson et al. 1958 (guinea pig)	Moderate	
Torkelson et al. 1958 (guinea pig)	Moderate	
Truffert et al. 1977 (rat)	Moderate	
Inhalation chronic-duration exposure		
NCI 1977 (rat)	High	
NCI 1977 (mouse)	High	
Ohnishi et al. 2013 (rat)	High	High
Ohnishi et al. 2013 (mouse)	High	
Quast et al. 1988 (rat)	High	
Oral acute-duration exposure		
Torkelson et al. 1958 (mouse)	Moderate	Moderate
Torkelson et al. 1958 (guinea pig)	Moderate	
Oral intermediate-duration exposure		
Bruckner et al. 2001 (rat)	High	High
Oral chronic-duration exposure		
NCI 1977 (rat)	High	High
NCI 1977 (mouse)	High	
Human studies		
Kelafant et al. 1994	Moderate	
Gamberale and Hultengren 1973	High	
Muttray et al. 2000	High	
Torkelson et al. 1958	Low	

Table C-17. Initial Confidence Rating for 1,1,1-Trichloroethane Health Effects Studies

Reference	Initial study confidence	Initial confidence rating
Mackay et al. 1987	High	
Stewart et al. 1961	Moderate	
Stewart et al. 1969	Low	
Savolainen et al. 1981	High	
Salvini et al. 1971	High	
Maroni et al. 1977	Low	

C.6.2 Adjustment of the Confidence Rating

The initial confidence rating was then downgraded or upgraded depending on whether there were substantial issues that would decrease or increase confidence in the body of evidence. The nine properties of the body of evidence that were considered are listed below. The summaries of the assessment of the confidence in the body of evidence for neurological and hepatic effects are presented in Table C-18. If the confidence ratings for a particular outcome were based on more than one type of human study, then the highest confidence rating was used for subsequent analyses. An overview of the confidence in the body of evidence for all health effects associated with 1,1,1-trichloroethane exposure is presented in Table C-19.

Table C-18. Adjustments to the Initial Confidence in the Body of Evidence

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Outcome: Hepatic effects			
Animal studies	High	+1 Consistency in body of evidence +1 Dose response	High
Human studies	Moderate	+1 Consistency in body of evidence	High
Outcome: Neurological effects			
Animal studies	High	+1 Consistency in body of evidence	High
Human studies	High	+1 Consistency in body of evidence +1 Dose response	High

Table C-19. Confidence in the Body of Evidence for 1,1,1-Trichloroethane

	Confidence in body of evidence	
Outcome	Human studies	Animal studies
Hepatic effects	High	High
Neurological effects	High	High

Five properties of the body of evidence were considered to determine whether the confidence rating should be downgraded:

- **Risk of bias.** Evaluation of whether there is substantial risk of bias across most of the studies examining the outcome. This evaluation used the risk of bias tier groupings for individual studies examining a particular outcome (Tables C-8 and C-9). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for risk of bias:
  - No downgrade if most studies are in the risk of bias first tier
  - Downgrade one confidence level if most studies are in the risk of bias second tier
  - Downgrade two confidence levels if most studies are in the risk of bias third tier

- **Unexplained inconsistency.** Evaluation of whether there is inconsistency or large variability in the magnitude or direction of estimates of effect across studies that cannot be explained. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for unexplained inconsistency:
  - No downgrade if there is little inconsistency across studies or if only one study evaluated the outcome
  - Downgrade one confidence level if there is variability across studies in the magnitude or direction of the effect
  - Downgrade two confidence levels if there is substantial variability across studies in the magnitude or direct of the effect

- **Indirectness.** Evaluation of four factors that can affect the applicability, generalizability, and relevance of the studies:
  - Relevance of the animal model to human health—unless otherwise indicated, studies in rats, mice, and other mammalian species are considered relevant to humans
  - Directness of the endpoints to the primary health outcome—examples of secondary outcomes or nonspecific outcomes include organ weight in the absence of histopathology or clinical chemistry findings in the absence of target tissue effects
  - Nature of the exposure in human studies and route of administration in animal studies—inhalation, oral, and dermal exposure routes are considered relevant unless there are compelling data to the contrary
  - Duration of treatment in animal studies and length of time between exposure and outcome assessment in animal and prospective human studies—this should be considered on an outcome-specific basis

  Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for indirectness:
  - No downgrade if none of the factors are considered indirect
  - Downgrade one confidence level if one of the factors is considered indirect
  - Downgrade two confidence levels if two or more of the factors are considered indirect

- **Imprecision.** Evaluation of the narrowness of the effect size estimates and whether the studies have adequate statistical power. Data are considered imprecise when the ratio of the upper to lower 95% CIs for most studies is ≥10 for tests of ratio measures (e.g., odds ratios) and ≥100 for absolute measures (e.g., percent control response). Adequate statistical power is determined if the study can detect a potentially biologically meaningful difference between groups (20% change from control response for categorical data or risk ratio of 1.5 for continuous data). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for imprecision:
  - No downgrade if there are no serious imprecisions
  - Downgrade one confidence level for serious imprecisions
  - Downgrade two confidence levels for very serious imprecisions

- **Publication bias.** Evaluation of the concern that studies with statistically significant results are more likely to be published than studies without statistically significant results.
  - Downgrade one level of confidence for cases where there is serious concern with publication bias

Four properties of the body of evidence were considered to determine whether the confidence rating should be upgraded:

- **Large magnitude of effect.** Evaluation of whether the magnitude of effect is sufficiently large so that it is unlikely to have occurred as a result of bias from potential confounding factors.
  - Upgrade one confidence level if there is evidence of a large magnitude of effect in a few studies, provided that the studies have an overall low risk of bias and there is no serious unexplained inconsistency among the studies of similar dose or exposure levels; confidence can also be upgraded if there is one study examining the outcome, provided that the study has an overall low risk of bias

- **Dose response.** Evaluation of the dose-response relationships measured within a study and across studies. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level for evidence of a monotonic dose-response gradient
  - Upgrade one confidence level for evidence of a non-monotonic dose-response gradient where there is prior knowledge that supports a non-monotonic dose-response and a non-monotonic dose-response gradient is observed across studies

- **Plausible confounding or other residual biases.** This factor primarily applies to human studies and is an evaluation of unmeasured determinants of an outcome such as residual bias towards the null (e.g., "healthy worker" effect) or residual bias suggesting a spurious effect (e.g., recall bias). Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level for evidence that residual confounding or bias would underestimate an apparent association or treatment effect (i.e., bias toward the null) or suggest a spurious effect when results suggest no effect

- **Consistency in the body of evidence.** Evaluation of consistency across animal models and species, consistency across independent studies of different human populations and exposure scenarios, and consistency across human study types. Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level if there is a high degree of consistency in the database

C.7 TRANSLATE CONFIDENCE RATING INTO LEVEL OF EVIDENCE OF HEALTH EFFECTS

In the seventh step of the systematic review of the health effects data for 1,1,1-trichloroethane, the confidence in the body of evidence for specific outcomes was translated to a level of evidence rating. The level of evidence rating reflected the confidence in the body of evidence and the direction of the effect (i.e., toxicity or no toxicity); route-specific differences were noted. The level of evidence for health effects was rated on a five-point scale:

- **High level of evidence:** High confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Moderate level of evidence:** Moderate confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Low level of evidence:** Low confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Evidence of no health effect:** High confidence in the body of evidence that exposure to the substance is not associated with the health outcome
- **Inadequate evidence:** Low or moderate confidence in the body of evidence that exposure to the substance is not associated with the health outcome OR very low confidence in the body of evidence for an association between exposure to the substance and the health outcome

A summary of the level of evidence of health effects for 1,1,1-trichloroethane is presented in Table C-20.

Table C-20. Level of Evidence of Health Effects for 1,1,1-Trichloroethane

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human studies			
Hepatic effects	High	No Health Effect	Low
Neurological effects	High	Health Effect	High
Animal studies			
Hepatic effects	High	Health Effect	High
Neurological effects	High	Health Effect	High

C.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. For health effects, there were four hazard identification conclusion categories:

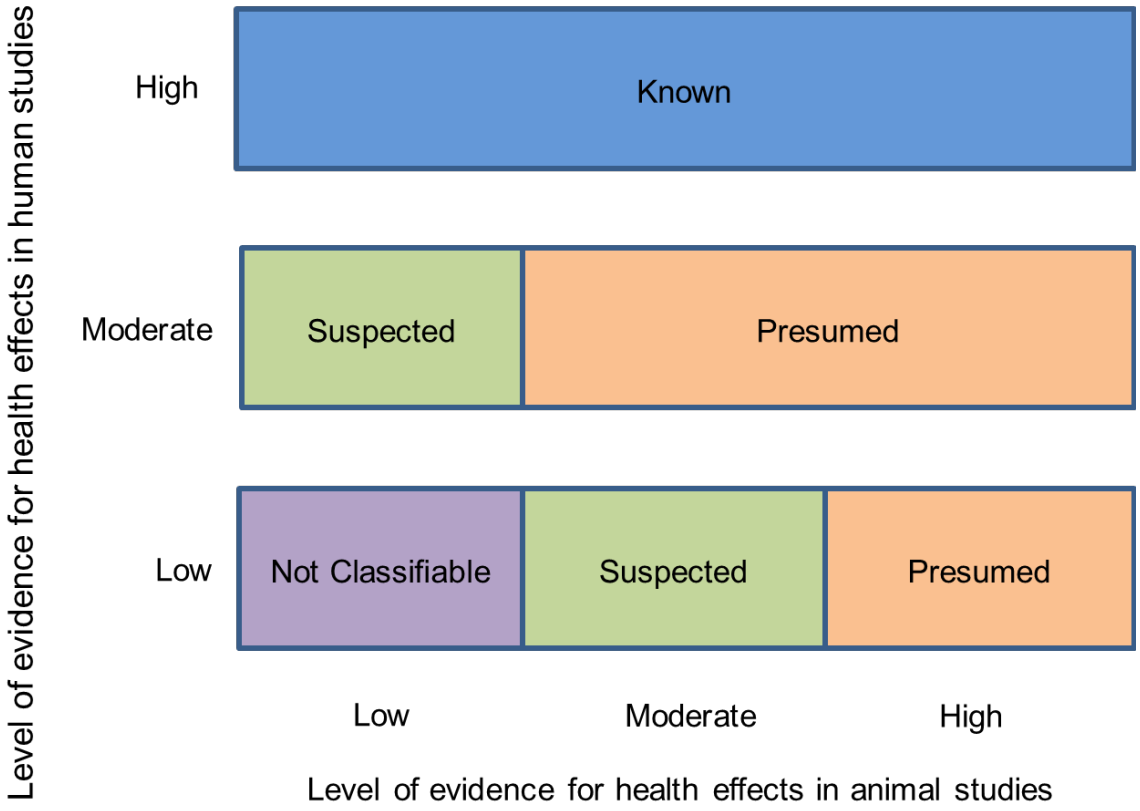
- **Known** to be a hazard to humans
- **Presumed** to be a hazard to humans
- **Suspected** to be a hazard to humans
- **Not classifiable** as to the hazard to humans

The initial hazard identification was based on the highest level of evidence in the human studies and the level of evidence in the animal studies; if there were no data for one evidence stream (human or animal), then the hazard identification was based on the one data stream (equivalent to treating the missing evidence stream as having low level of evidence). The hazard identification scheme is presented in Figure C-1 and described below:

- **Known:** A health effect in this category would have:
  - High level of evidence for health effects in human studies **AND** a high, moderate, or low level of evidence in animal studies.
- **Presumed:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** high or moderate level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** high level of evidence in animal studies
- **Suspected:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** low level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** moderate level of evidence in animal studies
- **Not classifiable:** A health effect in this category would have:
  - Low level of evidence in human studies **AND** low level of evidence in animal studies

Other relevant data such as mechanistic or mode-of-action data were considered to raise or lower the level of the hazard identification conclusion by providing information that supported or opposed biological plausibility.

Figure C-1. Hazard Identification Scheme



Two hazard identification conclusion categories were used when the data indicated that there may be no health effect in humans:

- **Not identified** to be a hazard in humans
- **Inadequate** to determine hazard to humans

If the human level of evidence conclusion of no health effect was supported by the animal evidence of no health effect, then the hazard identification conclusion category of "not identified" was used. If the human or animal level of evidence was considered inadequate, then a hazard identification conclusion category of "inadequate" was used. As with the hazard identification for health effects, the impact of other relevant data was also considered for no health effect data.

The hazard identification conclusions for 1,1,1-trichloroethane are listed below and summarized in Table C-21.

Presumed Health Effects

- Neurological
  - Inhalation of 1,1,1-trichloroethane in humans caused impaired performance on cognitive tests, and loss of consciousness (Gamberale and Hultengren 1973; Kelafant et al. 1994; Mackay et al. 1987; Savolainen et al. 1981). Oral exposure to 1,1,1-trichloroetane did not cause neurological effects (Stewart and Andrews 1966). Dermal occupational exposure resulted in alterations in peripheral nerve activity (Howse et al. 1989; Liss 1988).
  - In animal studies, inhalation of 1,1,1-trichloroethane resulted in effects like those seen in humans: impaired performance in behavioral tests, ataxia, and unconsciousness in monkeys, rats, and mice (Geller et al. 1982; Horiguchi and Horiuchi 1971; Kjellstrand et al. 1985a; Moser and Balster 1985, 1986; Moser et al. 1985; Mullin and Krivanek 1982; Páez-Martínez et al. 2003; Torkelson et al. 1958; Woolverton and Balster 1981). Neurophysiological changes including changes in flash-evoked potential and electroencephalogram and more subtle changes in somatosensory-evoked potential were also seen (Evans and Balster 1993).
  - Acute-duration oral exposure to 1,1,1-trichloroethane caused marked changes in flash-evoked potential and electroencephalogram, and smaller changes in somatosensory-evoked potential (Spencer et al. 1990). Intermediate-duration exposure to 1,1,1-trichloroethane resulted in hyperexcitability followed by narcosis (Bruckner et al. 2001). No significant effects were found as result of dermal exposure in animals (Torkelson et al. 1958).
  - Based on high evidence from animal studies and high evidence from human studies, the changes in brain physiology and deficits in cognitive and motor tests after inhalation exposure are classified as known health effects.
- Hepatic
  - A low level of evidence for hepatic effects from human studies exists after inhalation exposure to 1,1,1-trichloroethane as all studies showed little to no effect (Kelafant et al. 1994; Kramer et al. 1978). No studies that examined hepatic effects after oral or dermal exposure to 1,1,1-trichloroethane in humans were identified.
  - High level of evidence in animal studies from different species including rats, mice, rabbits, and guinea pigs. Histopathological changes and necrosis were observed in livers of mice, rats, and guinea pigs (McNutt et al. 1975; Torkelson et al. 1958) after acute-duration inhalation exposure. Intermediate-duration inhalation exposure to 1,1,1-trichloroethane also showed fatty degeneration in liver in rats and guinea pigs (Adams et al. 1950). Chronic-duration inhalation exposure in mice caused a dose-dependent increase incidence of hepatocellular adenoma (Ohnishi et al. 2013).

- Acute-duration exposure to 1,1,1-trichloroethane induced liver enzyme activity in rats and mice (Fuller et al. 1970; Koizumi et al. 1983; Lal and Shah 1970).
- Oral exposure to 1,1,1-trichloroethane induced mild hepatotoxicity, including changes in liver enzyme activity (Bruckner et al. 2001) and reduction in levels of cytochrome P-450 (Vainio et al. 1976). Dermal exposure to 1,1,1-trichloroethane increased liver enzymes in rats (Viola et al. 1981) but not in rabbits (Torkelson et al. 1958).
- Based on high evidence from animal studies and low evidence from human studies, hepatocellular changes resulting from inhalation exposure are classified as a presumed health effect.

Table C-21. Hazard Identification Conclusions for 1,1,1-Trichloroethane

Outcome	Hazard identification
Hepatic effects	Presumed
Neurological effects	Known

APPENDIX D. USER'S GUIDE

Chapter 1. Relevance to Public Health

This chapter provides an overview of U.S. exposures, a summary of health effects based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information, and an overview of the minimal risk levels. This is designed to present interpretive, weight-of-evidence discussions for human health endpoints 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?

Minimal Risk Levels (MRLs)

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

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Section 1.2, Summary of Health Effects, contains basic information known about the substance. Other sections, such as Section 3.2 Children and Other Populations that are Unusually Susceptible and Section 3.4 Interactions with Other Substances, provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive 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 no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a

substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables that are provided in Chapter 2. Detailed discussions of the MRLs are presented in Appendix A.

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species and MRLs to humans for noncancer endpoints. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE tables and figures follow. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

TABLE LEGEND

See Sample LSE Table (page D-5)

(1) Route of exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically, when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure (i.e., inhalation, oral, and dermal). LSE figures are limited to the inhalation and oral routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures. Profiles with more than one chemical may have more LSE tables and figures.

(2) Exposure period. Three exposure periods—acute (<15 days), intermediate (15–364 days), and chronic (≥365 days)—are presented within each relevant route of exposure. In this example, two oral studies of chronic-duration exposure are 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) Figure key. 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 51 identified NOAELs and less serious LOAELs (also see the three "51R" data points in sample LSE Figure 2-X).

(4) Species (strain) No./group. The test species (and strain), whether animal or human, are identified in this column. The column also contains information on the number of subjects and sex per group. Chapter 1, Relevance to Public Health, covers the relevance of animal data to human toxicity and Section 3.1, 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.

(5) Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 51), rats were orally exposed to “Chemical X” via feed for 2 years. For a

more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Aida et al. 1992).

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), food intake (FI), gross necropsy (GN), hematology (HE), histopathology (HP), immune function (IX), lethality (LE), neurological function (NX), organ function (OF), ophthalmology (OP), organ weight (OW), reproductive function (RX), urinalysis (UR), and water intake (WI).

(7) Endpoint. This column lists the endpoint examined. The major categories of health endpoints included in LSE tables and figures are death, body weight, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, developmental, other noncancer, and cancer. "Other noncancer" refers to any effect (e.g., alterations in blood glucose levels) not covered in these systems. In the example of key number 51, three endpoints (body weight, hematological, and hepatic) were investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. The body weight effect reported in key number 51 is a NOAEL at 25.5 mg/kg/day. NOAELs are not reported for cancer and death; with the exception of these two endpoints, this field is left blank if no NOAEL was identified in the study.

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. Key number 51 reports a less serious LOAEL of 6.1 mg/kg/day for the hepatic system, which was used to derive a chronic exposure, oral MRL of 0.008 mg/kg/day (see footnote "c"). MRLs are not derived from serious LOAELs. A 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. If no LOAEL/CEL values were identified in the study, this field is left blank.

(10) Reference. The complete reference citation is provided in Chapter 8 of the profile.

(11) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. For example, footnote "c" indicates that the LOAEL of 6.1 mg/kg/day in key number 51 was used to derive an oral MRL of 0.008 mg/kg/day.

FIGURE LEGEND

See Sample LSE Figure (page D-6)

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.

(12) Exposure period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the chronic exposure period are illustrated.

(13) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints appear in the LSE table.

(14) Levels of exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(15) LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).

(16) CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.

(17) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

APPENDIX D

Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral (1)

Figure key[a] (2, 3)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4	CS, WI, BW, OW, HE, BC, HP	Bd wt	25.5	138.0		Decreased body weight gain in males (23–25%) and females (31–39%)
					Hemato	138.0			
					Hepatic		6.1[c]		Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure
Aida et al. 1992 (10)									
52	Rat (F344) 78 M	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	Hepatic	36.3			
					Renal	20.6	36.3		Increased incidence of renal tubular cell hyperplasia
					Endocr	36.3			
George et al. 2002									
59	Rat (Wistar) 58M, 58F	Lifetime (W)	M: 0, 90 F: 0, 190	BW, HP	Cancer		190 F		Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided
Tumasonis et al. 1985									

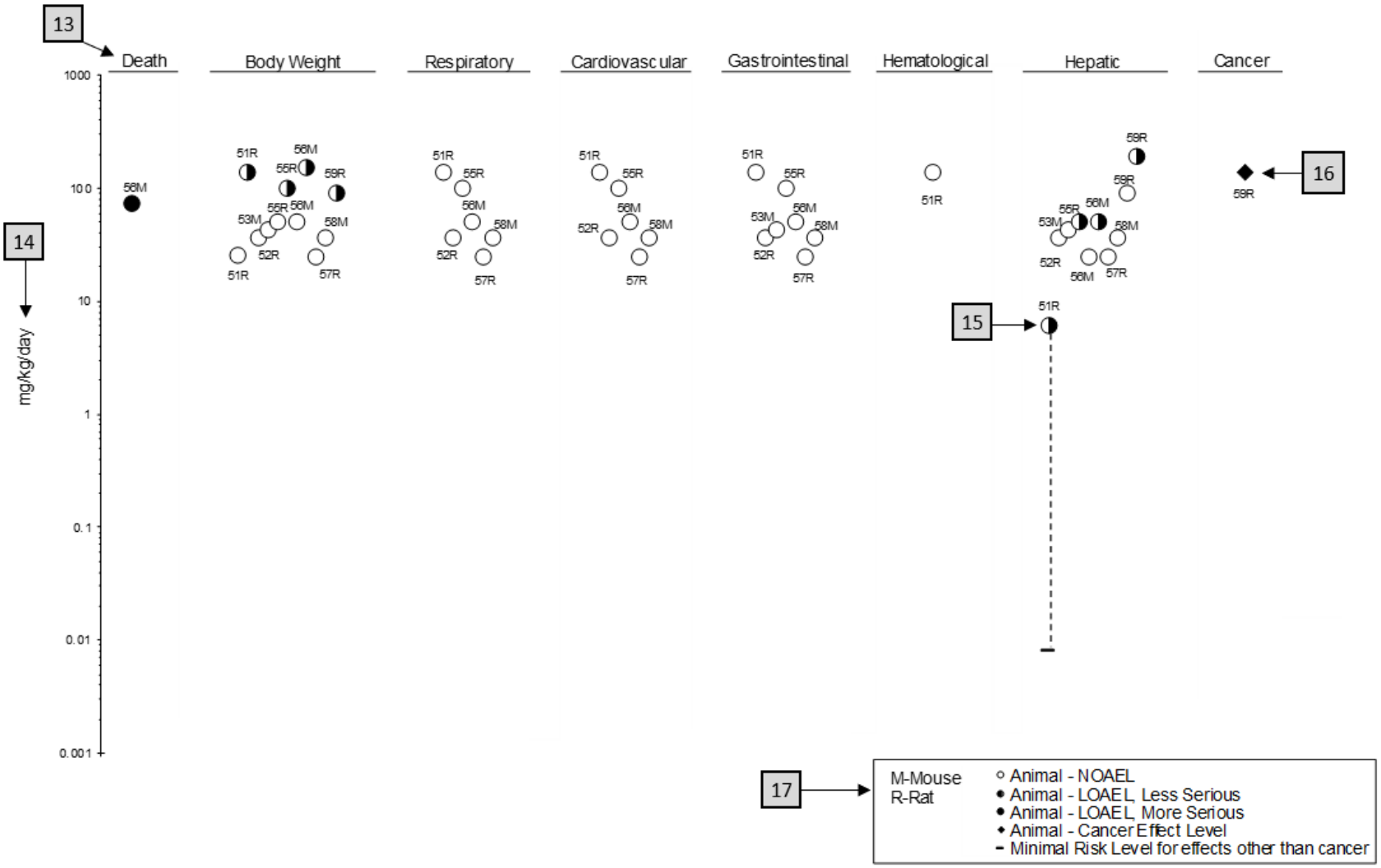
[a]The number corresponds to entries in Figure 2-x.

(11) [b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

APPENDIX D

Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral



APPENDIX E. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

Chapter 1: Relevance to Public Health: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

Chapter 2: Health Effects: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting.

Pediatrics:
Section 3.2 Children and Other Populations that are Unusually Susceptible
Section 3.3 Biomarkers of Exposure and Effect

ATSDR Information Center

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

ATSDR develops educational and informational materials for health care providers categorized by hazardous substance, clinical condition, and/or by susceptible population. The following additional materials are available online:

Clinician Briefs and Overviews discuss health effects and approaches to patient management in a brief/factsheet style. They are narrated PowerPoint presentations with Continuing Education credit available (see https://www.atsdr.cdc.gov/emes/health_professionals/clinician-briefs-overviews.html).

Managing Hazardous Materials Incidents is a set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.html).

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

Other Agencies and Organizations

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

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

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

Clinical Resources (Publicly Available Information)

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

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

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

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

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

APPENDIX F. GLOSSARY

Absorption—The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to the taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of ≤14 days, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD) or Benchmark Concentration (BMC)—is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a BMD_{10} would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

Cancer Effect Level (CEL)—The lowest dose of a chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or malignant tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

Case Report—A report that describes a single individual with a particular disease or exposure. These reports may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Reports that describe the experience of a small number of individuals with the same disease or exposure. These reports may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration that must not be exceeded.

Chronic Exposure—Exposure to a chemical for ≥365 days, as specified in the Toxicological Profiles.

Clastogen—A substance that causes breaks in chromosomes resulting in addition, deletion, or rearrangement of parts of the chromosome.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at a specific point in time.

Data Needs—Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the response or amount of the response.

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 effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

Epidemiology—The investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Excretion—The process by which metabolic waste products are removed from the body.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one-half of a quantity of a chemical from the body or environmental media.

Health Advisory—An estimate of acceptable drinking water levels for a chemical substance derived by EPA and 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)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

Immunotoxicity—Adverse effect on the functioning of the immune system that may result from exposure to chemical substances.

Incidence—The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

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

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

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

Metabolism—Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

Minimal LOAEL—Indicates a minimal adverse effect or a reduced capacity of an organ or system to absorb additional toxic stress that does not necessarily lead to the inability of the organ or system to function normally.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—The state of being diseased; the morbidity rate is the incidence or prevalence of a disease in a specific population.

Mortality—Death; the mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations, which are changes in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a hazardous substance.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Although effects may be produced at this dose, they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio that is greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic endpoints. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—A type of physiologically based dose-response model that is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which a group is followed over time and the pertinent observations are made on events occurring after the start of the study.

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation RfC is expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). RQs are (1) ≥1 pound or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

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

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio/Relative Risk—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio that is greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Serious LOAEL—A dose that evokes failure in a biological system and can lead to morbidity or mortality.

Short-Term Exposure Limit (STEL)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

Toxicokinetic—The absorption, distribution, metabolism, and elimination of toxic compounds in the living organism.

Toxics Release Inventory (TRI)—The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

Xenobiotic—Any substance that is foreign to the biological system.

APPENDIX G. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	American Association of Poison Control Centers
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ACMT	American College of Medical Toxicology
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AIC	Akaike's information criterion
AIHA	American Industrial Hygiene Association
ALT	alanine aminotransferase
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BCF	bioconcentration factor
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
C	centigrade
CAA	Clean Air Act
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
cm	centimeter
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
ERPG	emergency response planning guidelines
F	Fahrenheit
F1	first-filial generation
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FR	Federal Register

FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GGT	γ-glutamyl transferase
GRAS	generally recognized as safe
HEC	human equivalent concentration
HED	human equivalent dose
HHS	Department of Health and Human Services
HPLC	high-performance liquid chromatography
HSDB	Hazardous Substances Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactate dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Level of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
MRL	Minimal Risk Level
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
Mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NCEH	National Center for Environmental Health
ND	not detected
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences

NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEHSU	Pediatric Environmental Health Specialty Unit
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
REL-C	recommended exposure limit-ceiling value
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SLOAEL	serious lowest-observed-adverse-effect level
SMR	standardized mortality ratio
sRBC	sheep red blood cell
STEL	short term exposure limit
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey

USNRC	U.S. Nuclear Regulatory Commission
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
µm	micrometer
µg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result