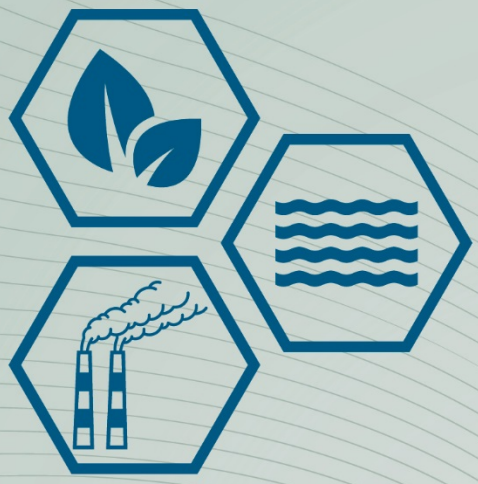

Toxicological Profile for 1,1,2-Trichloroethane

Draft for Public Comment

December 2019

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

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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 and EPA.

Each profile includes the following:

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

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine the levels of exposure that present a significant risk to human health due to acute, intermediate, and chronic duration exposures; 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. ATSDR plans to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Electronic comments may be submitted via: www.regulations.gov. Follow the on-line instructions for submitting comments.

Written comments may also be sent to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Human Health Sciences
Environmental Toxicology Branch
1600 Clifton Road, N.E.
Mail Stop S102-1
Atlanta, Georgia 30329-4027

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

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

Patrick N. Breysse, Ph.D., CIH
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Centers for Disease Control and Prevention

VERSION HISTORY

Date	Description
December 2019	Update of data in Chapters 2, 3, and 7
October 2010	Addendum to the toxicological profile released
December 1989	Final toxicological profile released

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These experts collectively have knowledge of toxicology, chemistry, and/or health effects. All reviewers were selected in conformity with Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

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.

CONTENTS

LIST OF FIGURES

LIST OF TABLES

CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

ATSDR's *Toxicological Profile for 1,1,2-Trichloroethane* was released in 1989, and *Addendum to the Toxicological Profile for 1,1,2-Trichloroethane* was released in 2010. In order to update the literature in this profile, ATSDR conducted a literature search focused on health effects information as described in Appendix B. Chapters 2 and 3 were revised to reflect the most current health effects data. In some cases, other sections of the profile were updated as needed or for consistency with the updated health effects data. However, the focus of the update to this profile is on health effects information.

1,1,2-Trichloroethane (CASRN 79-00-5) is predominantly a man-made chemical whose presence in the environment results from anthropogenic activity. This chemical is an intermediate in the biodegradation of 1,1,2,2-tetrachloroethane. It is made commercially by the chlorination of ethylene with chlorine or by the oxychlorination of ethylene with hydrogen chloride (HCl) and oxygen. It is primarily used as a captive intermediate in the production of 1,1-dichloroethene (vinylidene chloride), but may also be used as a solvent, especially in chlorinated rubber manufacture but also for fats, oils, waxes, and resins (Hawley 1981).

The general population may be exposed to 1,1,2-trichloroethane through inhalation from indoor sources, including paints, adhesives, and cleaning agents. This chemical is also released into the air by vent gas and fugitive emissions from the production and use of 1,1,2-trichloroethane as well as volatilization from waste water and municipal treatment plants. Although 1,1,2-trichloroethane is found in the effluent from laundries and organic chemicals and mechanical products industries, exposure to 1,1,2-trichloroethane from contaminated drinking water is uncommon (Westrick et al. 1984). Few data with respect to the release of 1,1,2-trichloroethane to soil are available, but these releases are expected to involve the landfilling of sludge and process residues.

Because of 1,1,2-trichloroethane's short half-life, it is difficult to describe exposure using traditional biomarkers. In the 2003–2004, 2005–2006, 2007–2008, 2009–2010, and 2011–2012 National Health and Nutrition Examination Survey (NHANES), levels of blood 1,1,2-trichloroethane were less than the limit of detection using participants' whole blood sample (CDC 2017). Levels below the limit of detection or trace amounts of 1,1,2-trichloroethane have been reported in exhaled air (Wallace et al. 1984). Low levels of 1,1,2-trichloroethane were likewise detected in the tissues of people exposed primarily via inhalation (Bauer 1981a, 1981b).

1.2 SUMMARY OF HEALTH EFFECTS

Studies in humans are confined to dermal irritation studies, and studies of occupational or residential exposures to 1,1,2-trichloroethane, all of which are confounded by exposure to other chemicals. Therefore, all implications of public health are derived from animal studies. Information on the toxicity of 1,1,2-trichloroethane comes primarily from acute-duration (up to 14 days in rats, mice, and dogs) and intermediate-duration (up to 13 weeks in rats and mice) oral studies and acute-duration inhalation studies. Several intermediate-duration and chronic-duration (78 weeks in rats and mice) oral toxicity studies in animals are also available. Only one well-conducted intermediate-duration (13 weeks) inhalation toxicity study is available. Data integration involved evaluating all of the animal toxicity data, determining effects levels for the endpoints evaluated in these studies, and determining the effects that were observed at the lowest concentrations/doses. As illustrated in Figure 1-1 and Figure 1-2, the most sensitive effects appear to be respiratory effects, liver damage, impaired immune response, and neurological effects. A systematic review of these endpoints resulted in the following hazard identification conclusions (see also Appendix C, Section C.8):

- Respiratory effects following inhalation exposure are a presumed health effect for humans
- Hepatic effects are a presumed health effect for humans
- Neurological effects following acute exposure are a presumed health effect for humans
- Immunological effects are a suspected health effect for humans

Respiratory Effects. There were no studies in humans for this endpoint. In laboratory animals, acute- and intermediate-duration inhalation studies in rats and acute-, intermediate-, and/or chronic-duration studies in rats and mice were available. Rats exposed to 1,1,2-trichloroethane for 4 hours showed increased protein content in bronchoalveolar lavage at 1,473 ppm (males) and 840 ppm (females) and necrosis of the olfactory epithelium at ≥58 ppm; the incidence and severity of these lesions increased in an exposure-related manner (Kirkpatrick 2001). In the only intermediate-duration inhalation toxicity study available, rats exposed at ≥40 ppm for 13 weeks showed significantly increased incidences of lesions in the olfactory epithelium of the nasal turbinates, including atrophy, vacuolization and microcyst formation, and respiratory epithelial metaplasia compared to control rats (Kirkpatrick 2002). In oral studies, there were no effects on lung weight in mice exposed via gavage at up to 38 mg/kg/day for 14 days or 305 mg/kg/day (males) or 384 mg/kg/day (females) for 90 days (White et al. 1985). In

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

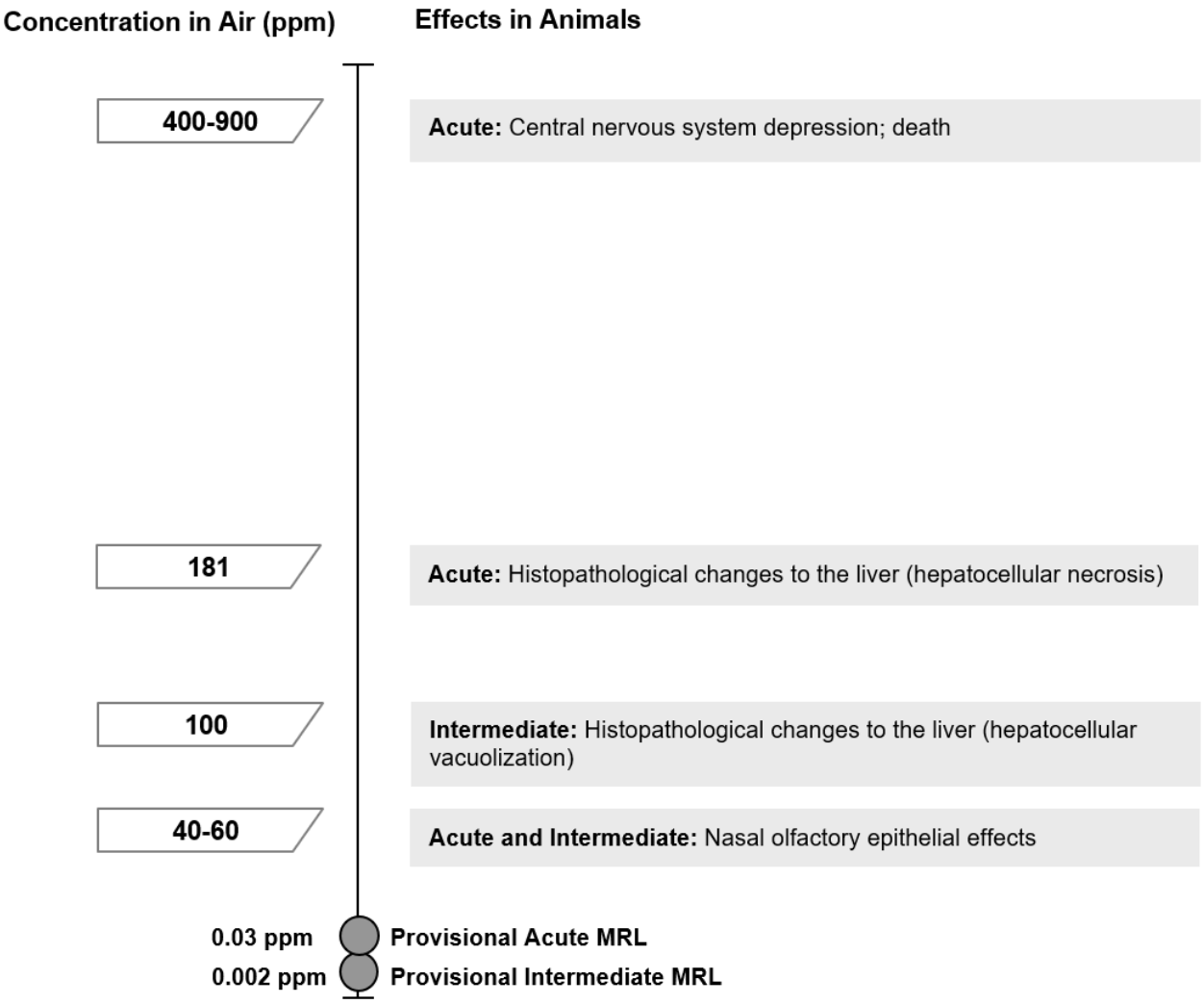
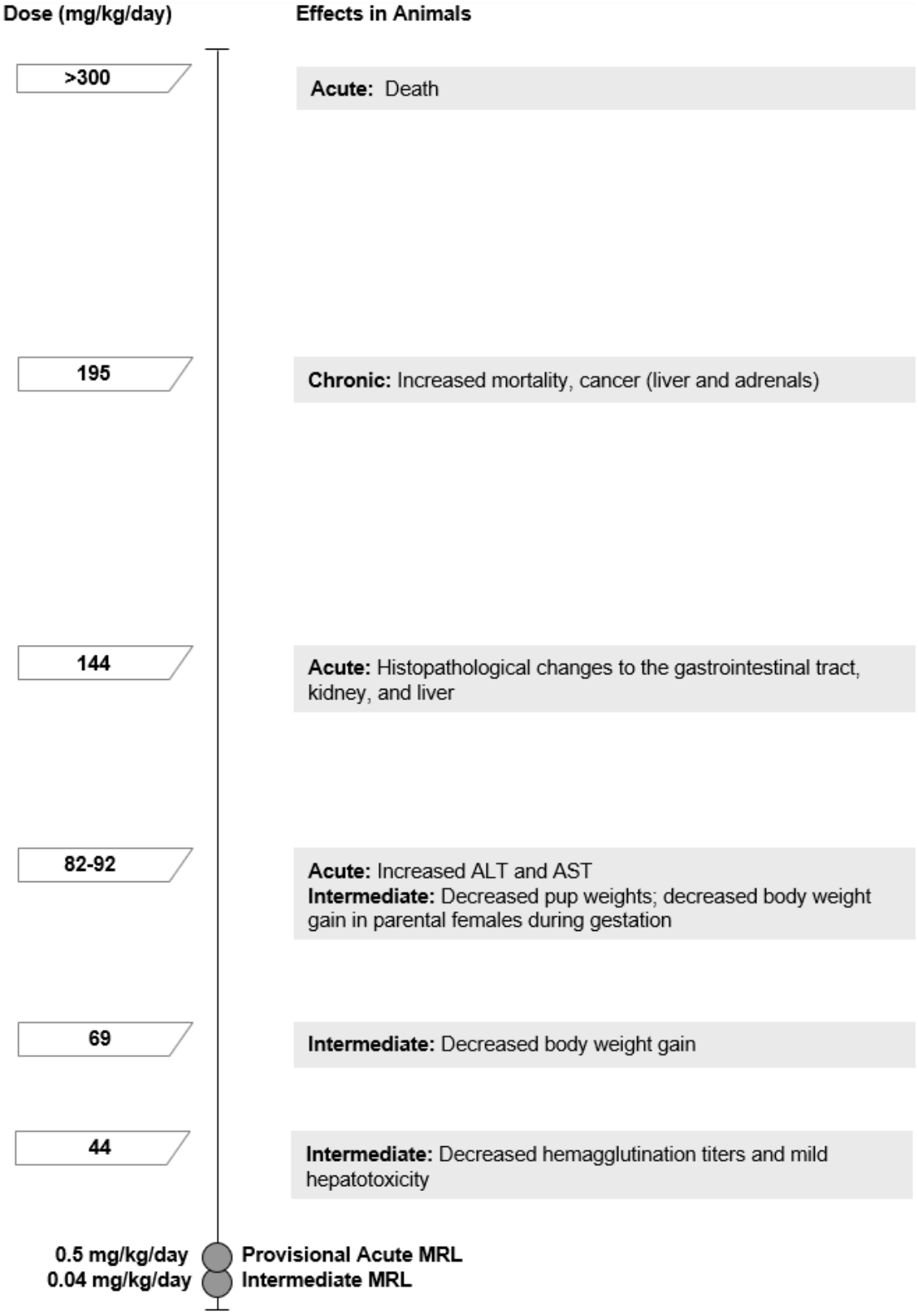


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to 1,1,2-Trichloroethane



78-week studies, no non-neoplastic respiratory tract lesions were observed at up to 92 mg/kg/day (rats) or 390 mg/kg/day (mice) (NCI 1978). It is probable that respiratory effects (seen in animal inhalation toxicity studies that performed histological examinations) could also be produced in humans exposed to 1,1,2-trichloroethane, although there are no data currently available indicating respiratory effects in humans.

Hepatic Effects. There were no studies in humans for this endpoint. In laboratory animals, acute- and intermediate-duration inhalation studies in rats and mice, and acute-, intermediate-, and/or chronic-duration studies in rats, mice, and dogs were available. Rats and mice acutely exposed to 1,1,2-trichloroethane (for 2–15 hours) showed increased alanine aminotransferase (ALT) levels at ≥2,080 ppm in rats and 800 ppm in mice (Carlson 1973; Gehring 1968; Takahara 1986a). Histopathological liver effects (hepatocellular vacuolization or necrosis) were also reported in rats exposed to 1,1,2-trichloroethane at ≥181 ppm for 4 hours (Kirkpatrick 2001) and in rats exposed at 100 ppm for 13 weeks (Kirkpatrick 2002). In oral studies, increased aspartate aminotransferase (AST) and ALT were among the most frequently observed effects in rats and mice following acute- (1–14 days of exposure at ≥~92 mg/kg/day) or intermediate-duration (90 days at 384 mg/kg/day) exposure to 1,1,2-trichloroethane (Moody and Smuckler 1986; Moody et al. 1981; Platt and Cockrill 1969; Tyson et al. 1983; White et al. 1985; Xia and Yu 1992). Histopathological changes (mild congestion, fatty acid degeneration, edema) were observed in dogs treated at a single dose of ≥144 mg/kg/day (Wright and Schaffer 1932), and increased liver weights were reported in female mice administered 384 mg/kg/day for 90 days (White et al. 1985). In the 90-day study by White et al. (1985), a sex difference in susceptibility to 1,1,2-trichloroethane was reported. Male mice showed decreased glutathione levels and females showed increased glutathione and a significant increase in ALT. Mechanistic data from *in vitro* and *ex vivo* studies suggest that the formation of free radicals may play a significant part in the mechanism of hepatotoxicity of 1,1,2-trichloroethane (Albano et al. 1985; Xia and Yu 1992). It is probable that hepatic effects (identified in numerous acute- and intermediate-duration animal toxicity studies) could also be produced in humans exposed to 1,1,2-trichloroethane, although there are no data currently available indicating hepatic effects in humans.

Immunological Effects. There were no studies in humans for this endpoint. In laboratory animals, acute- and intermediate-duration oral toxicity studies in mice were available. Studies of the effects of 1,1,2-trichloroethane on the immune system were performed by Sanders et al. (1985). In the acute-duration study, mice administered 1,1,2-trichloroethane by gavage at up to 38 mg/kg/day for 14 days showed no significant effects on humoral or cell-mediated immune endpoints; however, a limited number of evaluations were performed. A more comprehensive intermediate-duration (90 days) drinking water

study identified a significant reduction in hemagglutination titers in male mice at ≥46 mg/kg/day and in female mice at ≥44 mg/kg/day. Macrophage phagocytic activity was also affected in males treated at higher doses, while endpoints evaluating the cell-mediated immune response in both sexes were unaffected by treatment. Chronic-duration (78 weeks) studies in mice and rats identified no-observed-adverse-effect levels (NOAELs) for immunological effects of 390 and 92 mg/kg/day, respectively, based on the absence of histological changes (to the spleen, thymus, bone marrow, or lymph nodes), but immunological function was not evaluated. These data suggest that 1,1,2-trichloroethane may interfere with immune function in animals. The 90-day study by Sanders et al. (1985) also showed a sex difference in the response to 1,1,2-trichloroethane in mice. Male mice showed a decreased ability to phagocytize sheep red blood cells (sRBCs), whereas females showed increased vascular clearance of sRBCs by the fixed macrophages of the reticuloendothelial system. It is possible that immune effects (seen in a limited capacity in animal oral toxicity studies) could also be produced in humans exposed to 1,1,2-trichloroethane, although there are no data currently available indicating immune system effects in humans.

Neurological Effects. There were no studies in humans for this endpoint. In laboratory animals, acute-duration oral and inhalation toxicity studies were available. Signs of central nervous system depression (anesthesia, sedation, and sleepiness) have been reported following acute-duration inhalation (2–15 hours) exposure to 1,1,2-trichloroethane in rats (at ≥840 ppm) and mice (at ≥418 ppm) (Bonnet et al. 1980; De Ceaurriz et al. 1981; Gehring 1968; Kirkpatrick 2001; Lazarew 1929). These types of effects were also observed after acute-duration oral exposure at ≥450 mg/kg in mice and 289–722 mg/kg in dogs (White et al. 1985; Wright and Schaffer 1932). One study identified gait impairment in rats administered a single gavage dose of 1,1,2-trichloroethane (in 10 mL/kg corn oil) at 200 mg/kg (Beck 2004); motor impairment was noted in mice given 1,1,2-trichloroethane by gavage at 128 mg/kg (Borzelleca 1983). Taste aversion, which represents a conditioned avoidance response following repetitive conditioning trials, was another neurological effect produced by 7 days of exposure to 1,1,2-trichloroethane at 100 mg/kg/day (Kallman et al. 1983). No data on neurological effects of 1,1,2-trichloroethane in humans were located, but the evidence in animals (from numerous acute-duration inhalation toxicity studies in rats and mice) suggests that this compound may have central nervous depressant effects in humans as well.

Cancer. With respect to studies in humans, a study by Dosemeci et al. (1999) contained data for this endpoint. This study evaluated the risks of renal cell carcinoma (RCC) caused by occupational exposures to various solvents and found no significant differences in RCC risk from exposure to 1,1,2-trichloroethane compared to control population (RCC risk was significantly increased from exposure to chlorinated solvents in general). The study is limited by a small sample size (687 respondents, including

only 23 with any exposure to 1,1,2-trichloroethane), and indirect measures of exposure. In laboratory animals, chronic-duration oral and dermal toxicity studies were available in rats and mice. Among animals, 1,1,2-trichloroethane was carcinogenic in mice, but not rats. 1,1,2-Trichloroethane induced increased incidences of hepatocellular carcinomas and adrenal pheochromocytomas (not specified as benign or malignant) in mice after exposure for 78 weeks (NCI 1978). Data from a subcutaneous carcinogenicity study in Sprague-Dawley rats conducted by Norpoth et al. (1988) found that treatment with 15.37 or 46.77 µmol 1,1,2-trichloroethane (approximately 2.05 or 6.24 mg) once per week for 2 years had no significant effect on the incidence of benign mesenchymal and epithelial tumors at any site. Although there was a dose-related increased incidence of sarcomas in treated rats of both sexes compared to untreated controls, no sarcomas were observed in untreated controls (based on data for 35 males and 50 females), and this effect was not significant based on comparison to vehicle-only (dimethyl sulfoxide [DMSO]) controls. Based on references cited in the study report, the spontaneous incidence of sarcomas in this strain of rats ranges between 1/16 and 2/4 in males and 4/36 and 2/13 for females. A cancer initiation and promotion study in rats was also negative (Story et al. 1986). The mechanism of 1,1,2-trichloroethane carcinogenicity in mice is not known; however, free radicals and aryl chlorides (including chloroacetic acid) generated from P-450-mediated metabolism of 1,1,2-trichloroethane and deoxyribonucleic acid (DNA) adduct formation may play a role in tumor formation (Mazzullo et al. 1986; Yllner 1971). From the limited evidence in mice, 1,1,2-trichloroethane has been classified in Group C as a possible carcinogen (EPA 1988a). The International Agency for Research on Cancer (IARC 1999) classified the chemical as Group 3, not classifiable as to carcinogenicity in humans.

1.3 MINIMAL RISK LEVELS (MRLs)

As presented in Figure 1-3, limited inhalation data from animals indicate respiratory, hepatic, and neurological systems as particularly sensitive targets of 1,1,2-trichloroethane toxicity. The provisional MRLs for acute- and intermediate-duration inhalation exposure to 1,1,2-trichloroethane are summarized in Table 1-1 and discussed in greater detail in Appendix A. No chronic inhalation studies were identified. As presented in Figure 1-4, available oral data in animals identify hepatic, immunological, and neurological systems as the most sensitive targets of 1,1,2-trichloroethane toxicity. The MRL values for acute- (provisional) and intermediate-duration oral exposure to 1,1,2-trichloroethane are summarized in Table 1-1 and discussed in greater detail in Appendix A. The available data were not considered adequate for derivation of a chronic-duration oral MRL.

Figure 1-3. Summary of Sensitive Targets of 1,1,2-Trichloroethane – Inhalation

The respiratory system is the most sensitive target of 1,1,2-trichloroethane inhalation exposure.
Numbers in circles are the lowest LOAELs for all health effects in animals; no human data were identified.

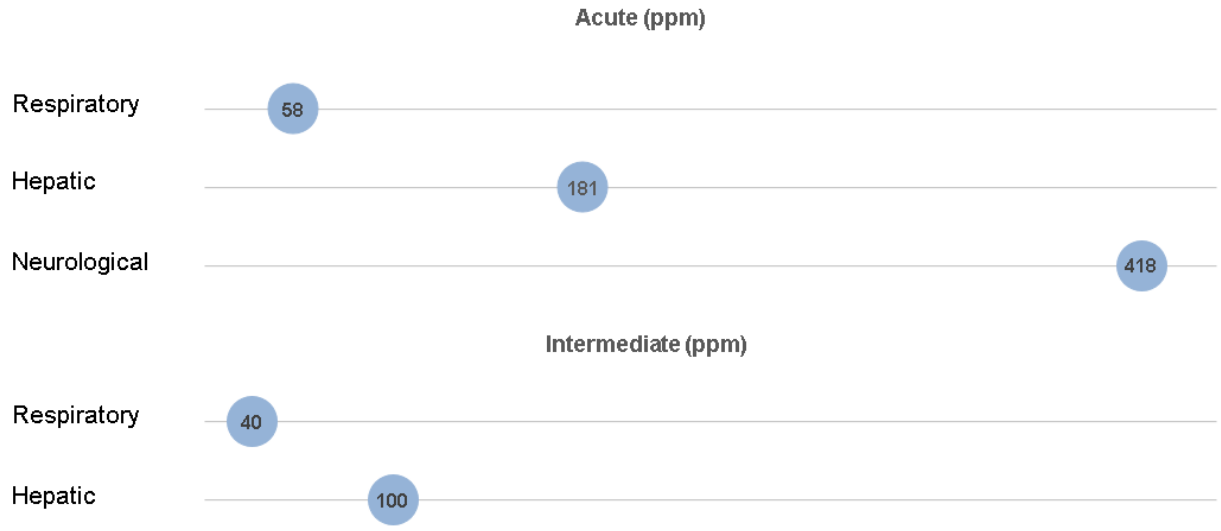


Table 1-1. Minimal Risk Levels (MRLs) for 1,1,2-Trichloroethane[a]

Exposure duration	MRL	Critical effect	Point of departure	Uncertainty factor	Reference
Inhalation exposure (ppm)					
Acute	0.03[b]	Necrosis of the olfactory epithelium	7.5 ($LOAEL_{[HEC]}$)	270	Kirkpatrick 2001
Intermediate	0.002[b]	Lesions of the olfactory epithelium	0.07 ($BMDL_{10[HEC]}$)	30	Kirkpatrick 2002
Chronic	Insufficient data for MRL derivation				
Oral exposure (mg/kg/day)					
Acute	0.5[b]	Increased ALT and AST	46 (NOAEL)	100	Tyson et al. 1983
Intermediate	0.04	Decreased hemagglutination titers and mild hepatotoxicity	3.9 (NOAEL)	100	Sanders et al. 1985; White et al. 1985
Chronic	Insufficient data for MRL derivation				

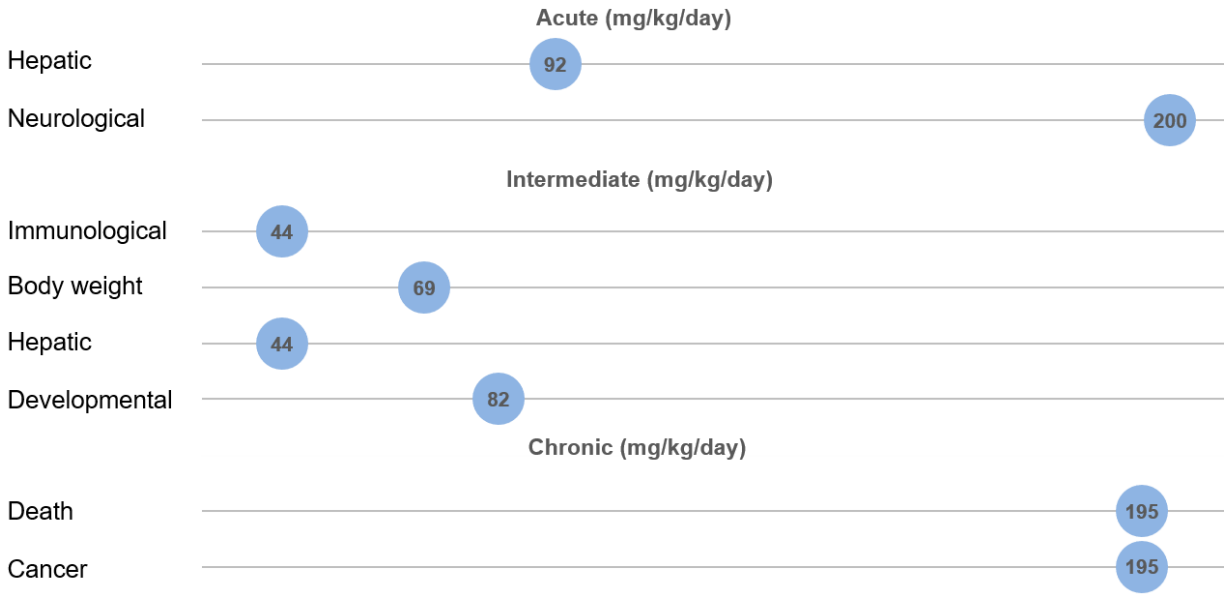
[a]See Appendix A for additional information.
[b]Provisional value.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMDL = lower confidence limit on the benchmark dose; HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

Figure 1-4. Summary of Sensitive Targets of 1,1,2-Trichloroethane – Oral

The immunological and hepatic systems are the most sensitive targets of 1,1,2-trichloroethane oral exposure.

Numbers in circles are the lowest LOAELs for all health effects in animals.
No reliable dose response data were available for humans.



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 1,1,2-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 1,1,2-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 1,1,2-trichloroethane was also conducted; the results of this review are presented in Appendix C.

Levels of significant exposure (LSEs) for each route and duration are presented in tables and illustrated in figures. Animal inhalation studies are presented in Table 2-1 and Figure 2-2, animal oral studies are presented in Table 2-2 and Figure 2-3, and human and animal dermal studies are presented in Table 2-3. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an 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. Levels of exposure associated with cancer (Cancer Effect Levels, CELs) of 1,1,2-trichloroethane are indicated in Table 2-2 and Figure 2-3.

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.

Most of the health effects data for 1,1,2-trichloroethane come from acute- and intermediate-duration oral studies and acute-duration inhalation studies in animals (Figure 2-1). In addition to the studies summarized in Figure 2-1, 16 studies examined lethality following inhalation, oral, or dermal exposure. One intermediate-duration inhalation toxicity study is available. Only four studies evaluated immunological endpoints; reproduction and development were evaluated in three to four oral studies of 1,1,2-trichloroethane exposure.

The available animal data suggest the following sensitive targets of toxicity:

- **Respiratory Endpoint:** Respiratory effects are a presumed health effect for humans based on the findings of histopathological changes to the olfactory epithelium following acute- and intermediate-duration inhalation exposure in animals.

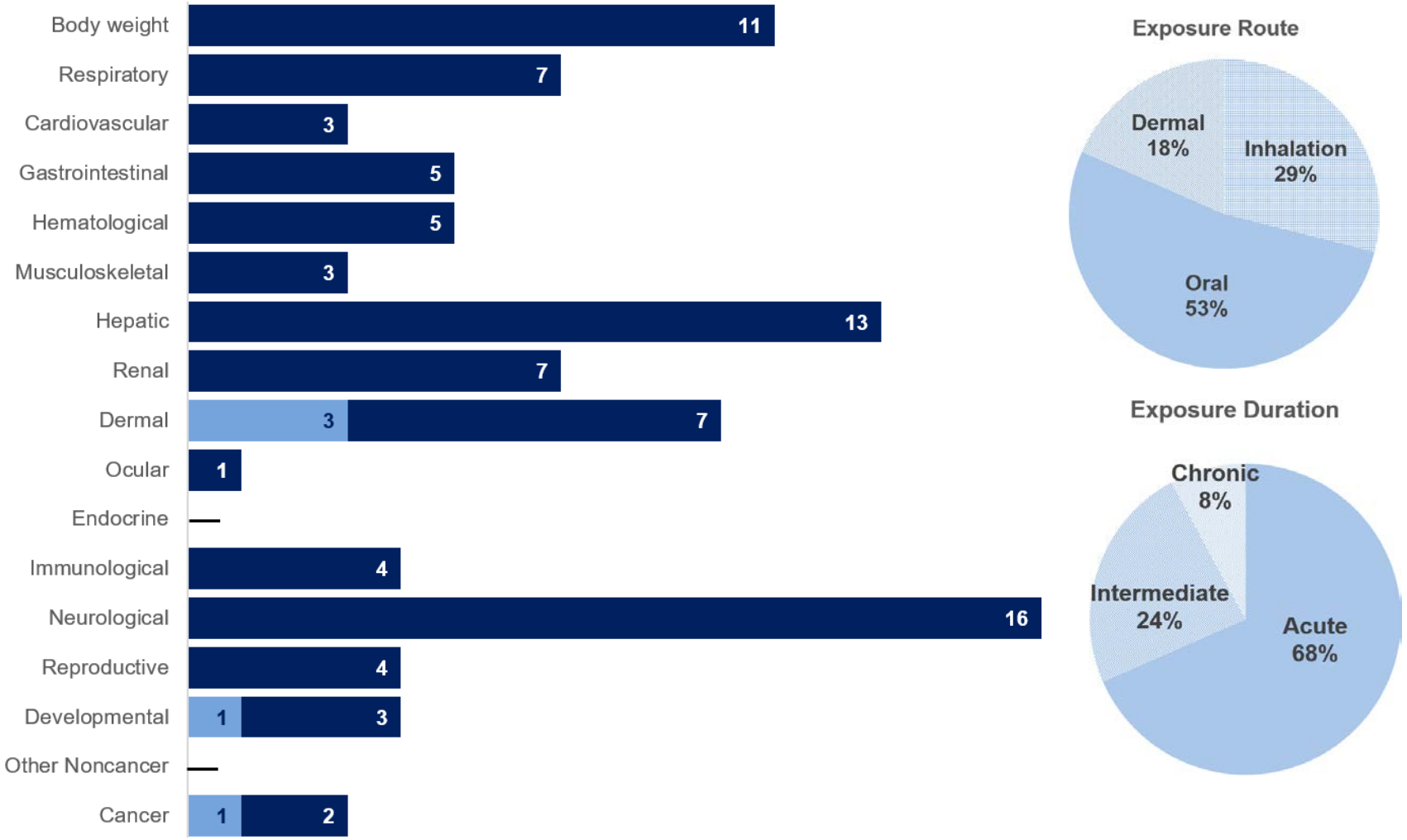
- **Hepatic Endpoint:** Hepatic effects are a presumed health effect for humans based on changes in the activities of liver enzymes (increased ALT and AST), biochemical changes (microsomal activities), and changes in liver pathology following oral and inhalation exposure in animals.

- **Neurological Endpoint:** Neurological effects following acute exposure are a presumed health effect in humans based on signs of central nervous system depression (sleepiness, loss of awareness, and sedation), taste aversion, and motor impairment following acute inhalation or oral exposure to 1,1,2-trichloroethane in animals.

- **Immunological Endpoint:** Immunological effects are a suspected health effect in humans based on the finding of decreased hemagglutination titers in an intermediate-duration oral exposure study in animals.

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

Most studies examined the potential body weight, hepatic, and neurological effects of 1,1,2-trichloroethane
Fewer studies evaluated health effects in **humans** than **animals** (counts represent studies examining endpoint)



*Includes studies discussed in Chapter 2. A total of 38 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effect
ACUTE EXPOSURE									
1	Rat (Sprague-Dawley) 12 M	6 hours	1,000–2,000	BW, GN, CS	Death			1,654	LC_{50}
					Neuro			1,654	Somnolent
Bonnet et al. 1980									
2	Rat (Albino) 5 M	2 hours	0, 890, 2,080	BW, OW, BC, BI	Death			2,080	3/5 died
					Hepatic	890	2,080		Increased ALT
Carlson 1973									
3	Rat (Sherman) 6 NS	4 hours	2,000	GN, HP, CS	Death			2,000	2–4/6 died
Carpenter et al. 1949									
4	Rat (Carworth Farms-Nelson) 6 F	8 hours	NR	CS	Death			999	LC_{50}
Pozzani et al. 1959									
5	Rat (Albino) 6 NS	8 hours	500	CS	Death			500	4/6 died
Smyth et al. 1969									
6	Rat (F344) 5 M, 5 F	4 hours	0, 58, 181, 1,527	BW, CS, GN, HP, LE, OW	Death			1,527 F	3/5 females died
					Resp		58[b]		Necrosis of the olfactory epithelium
					Hepatic	58		181	Hepatocellular necrosis
					Neuro			1,527	Sleepiness, decreased respiration
Kirkpatrick 2001									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effect
7	Rat (F344) 5 M, 5 F	4 hours	M: 0, 60, 205, 1,474 F: 0, 45, 170, 840	BI, BW, CS, LE	Death			840 F	3/5 females died
					Resp	205 M 170 F	1,474 M 840 F		Increased total protein content of BALF
					Neuro			1,474 M 840 F	Sleepiness, decreased respiration
Kirkpatrick 2001									
8	Mouse (Swiss OF_1) 10 M	4 hours	NR	CS	Neuro			418	CNS depression
De Ceaurriz et al. 1981									
9	Mouse (Swiss-Webster) 9–25 F	15 hours	0, 3,750	BC, CS	Death			3,750	Death
					Hepatic		3,750		Increased ALT
					Neuro			3,750	Anesthesia
Gehring 1968									
10	Mouse (OF_1 SPF) 20 F	6 hours	NR	CS	Death			416	LC_{50}
Gradiski et al. 1978									
11	Mouse (NS) NR	2 hours	NR	CS	Death			12,934	Death
					Neuro		1,833	2,749	Lie down on side (1,833 ppm); loss of reflex control (2,749 ppm)
Lazarew 1929									
12	Mouse (dd) 5 F	3 hours	800	BC, BI	Hepatic		800		Increased ALT and liver triglycerides; decreased plasma triglycerides and ATP
Takahara 1986a									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effect
INTERMEDIATE EXPOSURE									
13	Rat (F344 CDF Crl:BR) 10 M, 10 F	6 hours/ day 5 days/ week 13 weeks	0, 15, 40, 100	BC, BW, CS, FI, GN, HE, HP, LE, OP, OW	Bd wt	100			
					Resp	15[c]	40		Vacuolization/microcyst formation and atrophy of the olfactory epithelium
					Cardio	100			
					Gastro	100			
					Hemato	100			
					Musc/skel	100			
					Hepatic	40	100		Hepatocellular vacuolization
					Renal	100			
					Dermal	100			
					Ocular	100			
Kirkpatrick 2002									

[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 gender are presented.
[b]Used to derive a provisional acute-duration inhalation minimal risk level (MRL) of 0.03 ppm based on a $LOAEL_{[HEC]}$ of 7.5 ppm and an uncertainty factor of 270 (3 for the use of a minimal LOAEL, 3 for extrapolation from animals to humans,10 for human variability, and 3 for an incomplete database).
[c]Used to derive a provisional intermediate-duration inhalation minimal risk level (MRL) of 0.002 ppm based on a human equivalent $BMCL_{10}$ of 0.07 ppm and an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability).

ALT = alanine aminotransferase; ATP = adenosine triphosphate; BALF = bronchoalveolar lavage fluid; BC = serum (blood) chemistry; Bd wt or BW = body weight; BI = biochemical changes; Cardio = cardiovascular; CNS = central nervous system; CS = clinical signs; F = female(s); FI = food intake; Gastro = gastrointestinal; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; LC_{50} = lethal concentration, mortality 50%; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Neuro = neurological; NR = not reported; NS = not specified; OP = ophthalmology; OW = organ weight; Resp = respiratory

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

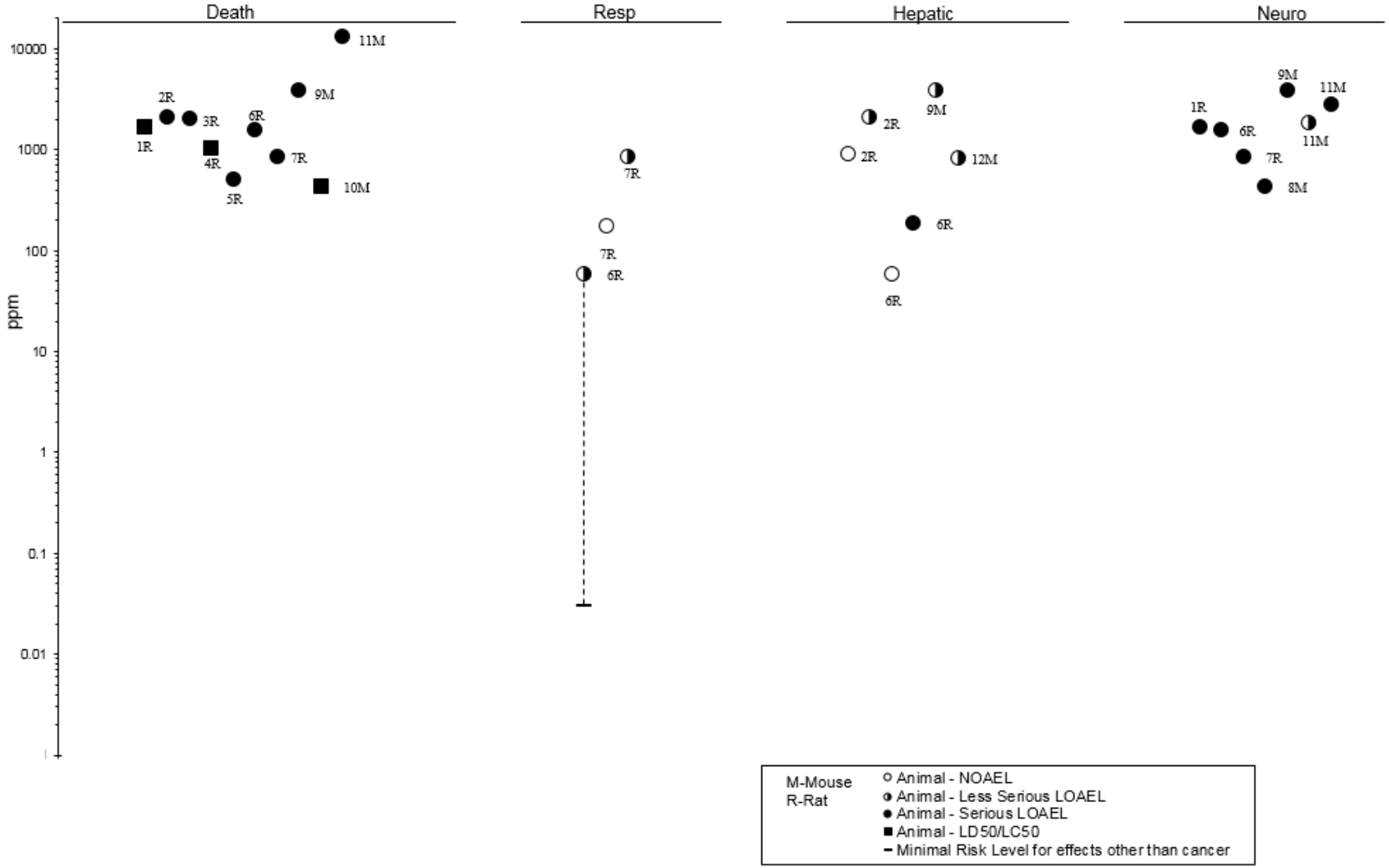


Figure 2-2. Levels of Significant Exposure to 1,1,2-Trichloroethane – Inhalation
Intermediate (15-364 days)

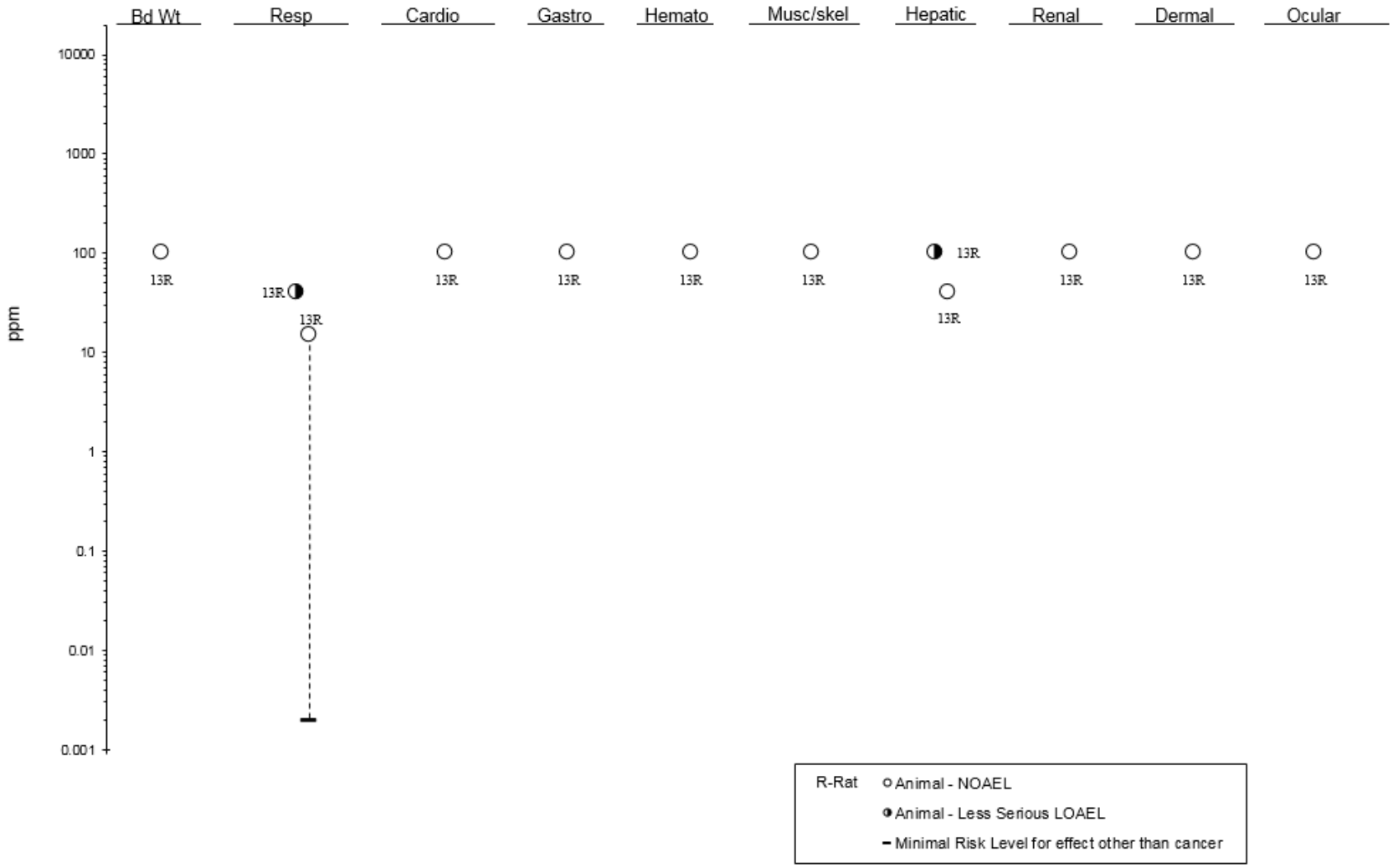


Table 2-2. Levels of Significant Exposure to 1,1,2-Trichloroethane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
ACUTE EXPOSURE									
1	Rat (Wistar-derived Alderley Park) 5 M	7 days (G)	0, 180	BW, OW, BI	Bd wt		180		Decreased body weight gain (19%)
					Hepatic	180			
Platt and Cockrill 1969									
2	Rat (Carworth-Wistar) 5 M	once (G)	NR	CS	Death			837	LD_{50}
Smyth et al. 1969									
3	Rat (Sprague-Dawley) 3–5 M	once (G)	0, 46, 92, 228[b]	BC	Hepatic	46[c]	92		Increased AST and ALT
Tyson et al. 1983									
4	Rat (Crl:CD (SD) IGS) 12 M, 12 F	once (GO)	0, 55, 95, 200	BH, BW, CS, HP, LE, OF, OW	Bd wt	95 M 200 F		200 M	Decreased body weight gain on days 0–7 (27%)
					Neuro	95	200		Gait impairment on study day 0 (4/12 males; 5/12 females; 0/12 controls)
Beck 2004									
5	Rat (Wistar) F NS	once (G)	667	BC	Hepatic		667		Increased ALT, SDH, glutamate dehydrogenase
Xia and Yu 1992									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
6	Mouse (CD-1) NR	once (G)	NR	CS	Neuro		128		Motor impairment
Borzelleca 1983									
7	Mouse (CD-1) 7 M	7 days (G)	3, 10, 30, 100, 300	WI, CS	Death			300	7/7 dead
					Neuro	30	100		Taste aversion to saccharin
Kallman et al. 1983									
8	Mouse (CD-1) 4 M	4 days (W)	0, 46	WI	Neuro	46			No taste aversion
Kallman and Kaempf 1984									
9	Mouse (CD-1) 11–12 M	14 days (G)	0, 3.8, 38	BW, OW, OF	Immuno	38			
Sanders et al. 1985									
10	Mouse (ICR/SIM) 30 F	5 days GDs 8–12 (G)	0, 350	BW, CS	Repro Develop	350 350			
Seidenberg et al. 1986									
11	Mouse (CD-1) 8 M	once (G)	200–600	GN, CS	Death			378 M 491 F	LD_{50}
					Gastro			200	Gastric irritation (animals that died)
					Neuro			450	Sedation
White et al. 1985									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
12	Mouse (CD-1) 12 M	14 days (G)	0, 3.8, 38	BW, OW, BC, CS, BI	Bd wt	38			
					Resp	38			No changes in lung weight
					Hemato	38			
					Hepatic	38			
					Renal	38			
White et al. 1985									
13	Dog (NS) 1–2 NS	Once	144, 289, 433, 722	GN, HP, CS	Death			722	1/1 died
					Gastro		144	433	Mild inflammation and congestion (144 mg/kg); hemorrhage (433 mg/kg)
					Hepatic		144	433	Mild congestion, fatty acid degeneration and edema (144 mg/kg); necrosis (433 mg/kg)
					Renal		144		Mild congestion and cloudy swelling
					Neuro	144		289	Drowsiness
Wright and Schaffer 1932									
INTERMEDIATE EXPOSURE									
14	Rat (F344/ DUCRL) 10 M, 10 F	13 weeks (W)	M: 0, 12.1, 37.7, 86.0 F: 0, 17.1, 55.9, 98.2	BH, BW, CS, FI, HP, OF, WI	Bd wt	98.2			
					Neuro	98.2			
Maurissen et al. 2005									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
15	Rat Crl:CD(SD) IGS 30 M, 30 F	2-generation (W)	Parental P1 and F1 (range): 0, 12.1–24.7, 40.6–82.5, 82.2–173	BW, CS, DX, FI, FX, GN, HP, OF	Bd wt Repro Develop	40.6 F 173 40.6	82.2 F 82.2		Decreased body weight gain during gestation in P1 and F1 females (12–17%) Decreased F1 and F2 pup weights on PNDs 4–21
Mylchreest 2006									
16	Rat (Crl:CD(SD)IGS BR) 25 F	GDs 6–20 (W)	0, 17, 48, 111	BW, CS, DX, FI, FX, LE, MX, OW, TG, WI	Bd wt Develop	48 111	111		Decreased body weight gain (13%)
Wilson 2005									
17	Rat (Osborne-Mendel) 10 M	7 weeks 5 days/week (G)	0, 69	BW, OW, HP	Bd wt		69		Decreased body weight gain (60%)
Story et al. 1986									
18	Mouse (CD-1) 8–25 M, 8–25 F	90 days (W)	M: 0, 4.4, 46, 305 F: 0, 3.9, 44, 384	BC, OF	Immuno	4.4 M 3.9 F[d]	46 M 44 F		Decreased hemagglutination titers
Sanders et al. 1985									
19	Mouse (CD-1) 32–48 M, 32–48 F	90 days (W)	M: 0, 4.4, 46, 305 F: 0, 3.9, 44, 384	BW, OW, WI, BC, HE, BI	Bd wt Resp Hemato Hepatic	46 M 384 F 305 M 384 F 305 M 384 F 4.4 M 3.9 F[d]	305 M 46 M 44 F		Decreased body weight gain (10%) No changes in lung weight Decreased glutathione (males); changes in microsomal enzyme activity (females)

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
					Renal	305 M 384 F			
White et al. 1985									
CHRONIC EXPOSURE									
20	Rat (Osborne-Mendel) 20–50 M, 20–50 F	78 weeks 5 days/week (G)	0, 46, 92	BW, GN, HP, CS	Bd wt	92			
					Resp	92			
					Cardio	92			
					Gastro	92			
					Hemato	92			No histological alterations
					Musc/skel	92			
					Hepatic	92			
					Renal	92			
					Dermal	92			
					Ocular	92			
					Immuno	92			No histological alterations
					Neuro	92			No histological alterations
					Repro	92			No histological alterations
					Cancer				No increase in neoplasms
NCI 1978									
21	Mouse (B6C3F1) 20–50 M, 20–50 F	78 weeks 5 days/week (G)	0, 195, 390	BW, GN, HP, CS	Death			195	Increased mortality
					Bd wt	390			
					Resp	390			
					Cardio	390			
					Gastro	390			
					Hemato	390			No histological alterations
					Musc/skel	390			
					Hepatic	390			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
					Renal	390			
					Dermal	390			
					Ocular	390			
					Immuno	390			No histological alterations
					Neuro	390			No histological alterations
					Repro	390			No histological alterations
					Cancer			195	CEL: hepatocellular carcinomas at ≥195 mg/kg and adrenal pheochromocytomas (not specified as benign or malignant) at 390 mg/kg

NCI 1978

[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 gender are presented.
[b]Doses were estimated from data presented graphically in the study report (Tyson et al. 1983) using GrabIt! Software.
[c]Used to derive a provisional acute oral Minimal Risk Level (MRL); dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability) resulting in a provisional oral MRL of 0.5 mg/kg/day.
[d]Used to derive an intermediate oral MRL; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) resulting in an MRL of 0.04 mg/kg/day.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BC = serum (blood) chemistry; Bd wt or BW = body weight; BH = behavioral; BI = biochemical changes; Cardio = cardiovascular; CEL = cancer effect level; CS = clinical signs; Develop = developmental; DX = developmental toxicity; F = female(s); FI = food intake; FX = fetal toxicity; (G) = gavage; Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; (GO) = gavage in oil; Hemato = hematological; HP = histopathology; Immuno = immunological; LD_{50} = lethal dose; 50% kill; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); Musc/skel = musculoskeletal; MX = maternal toxicity; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; NR = not reported; OF = organ function; OW = organ weight; PND = postnatal day; Repro = reproductive; Resp = respiratory; SDH = sorbitol dehydrogenase; TG = teratogenicity; (W) = drinking water; WI = water intake

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

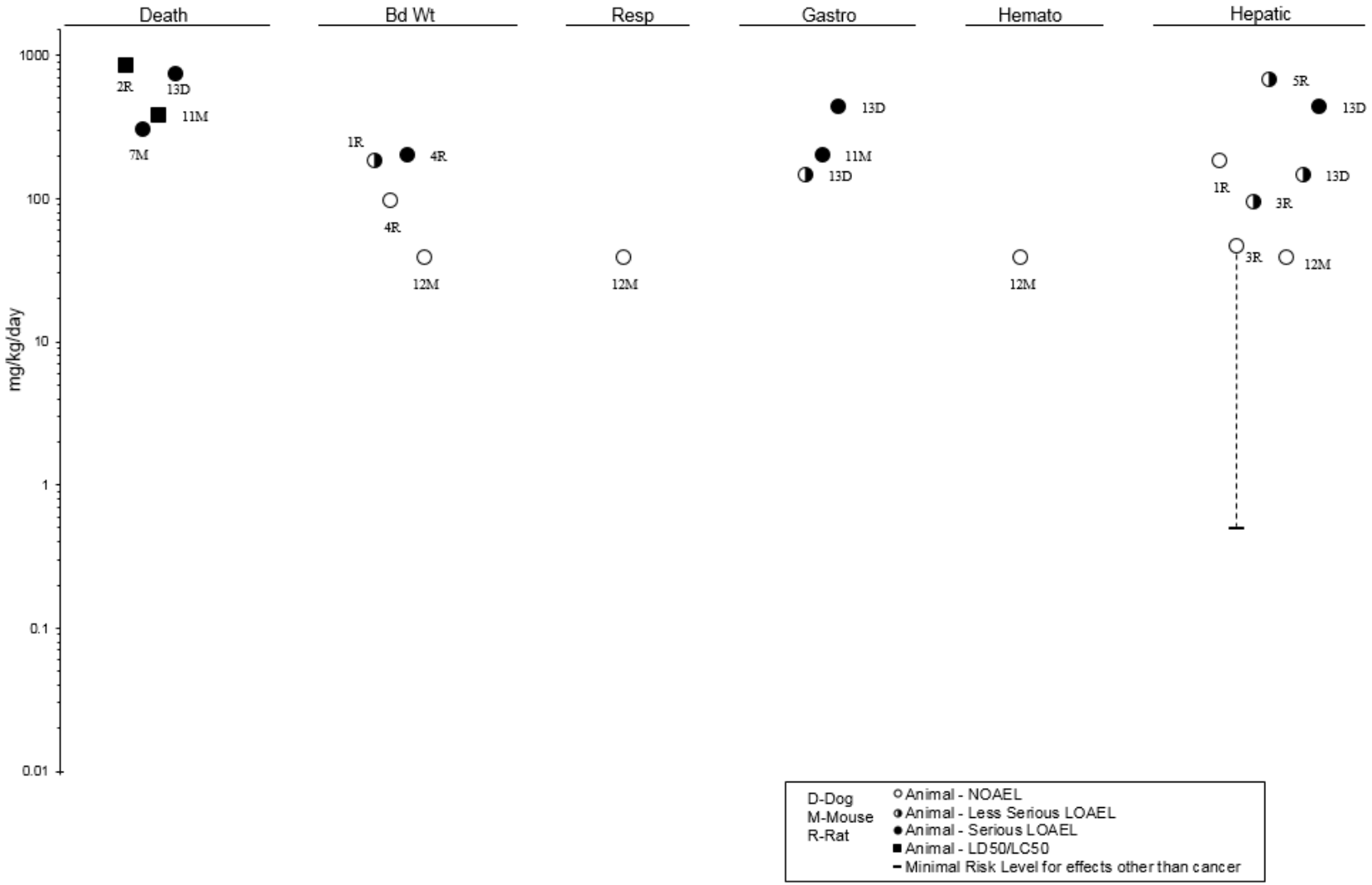


Figure 2-3. Levels of Significant Exposure to 1,1,2-Trichloroethane – Oral
Acute (≤14 days)

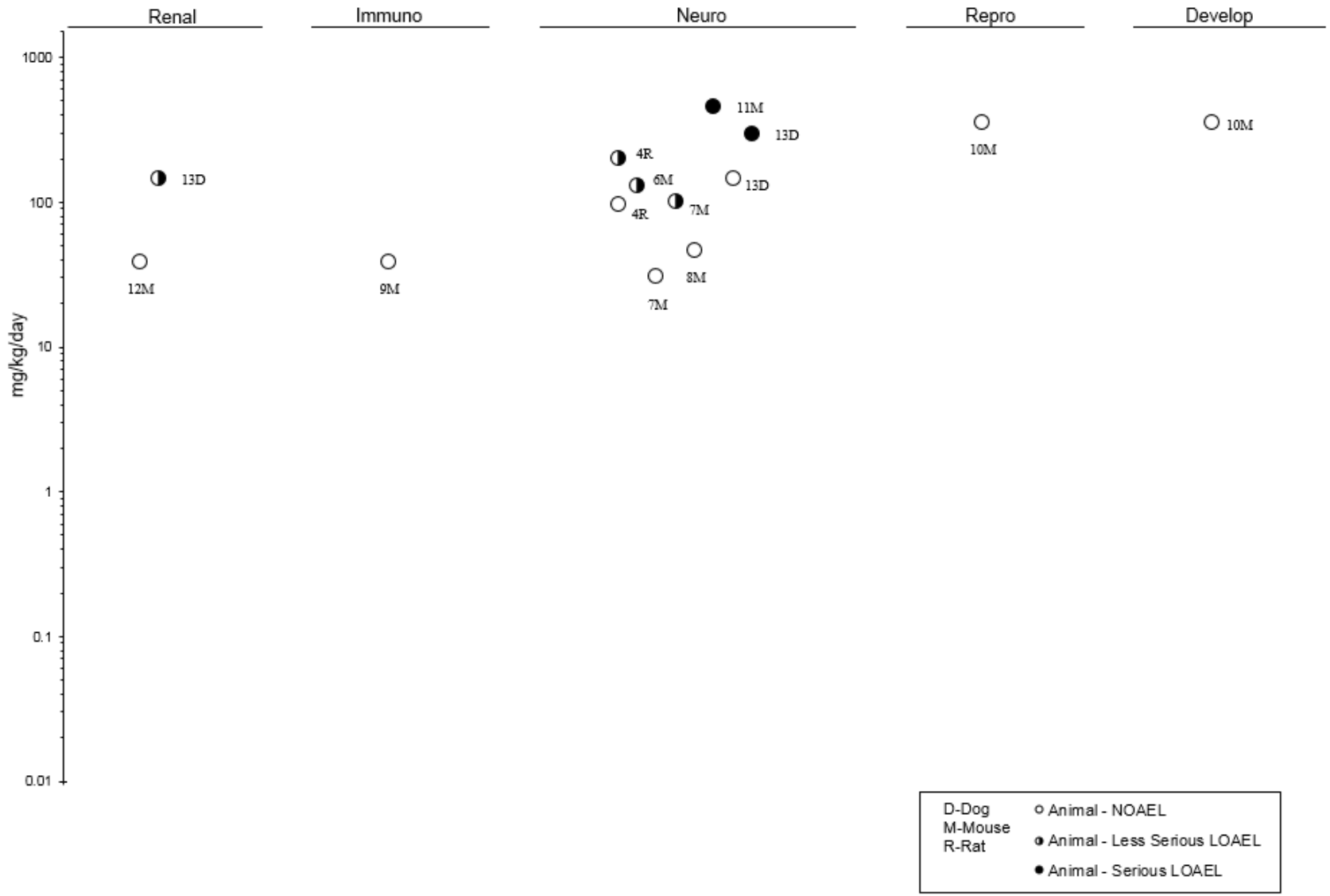


Figure 2-3. Levels of Significant Exposure to 1,1,2-Trichloroethane – Oral
Intermediate (15-364)

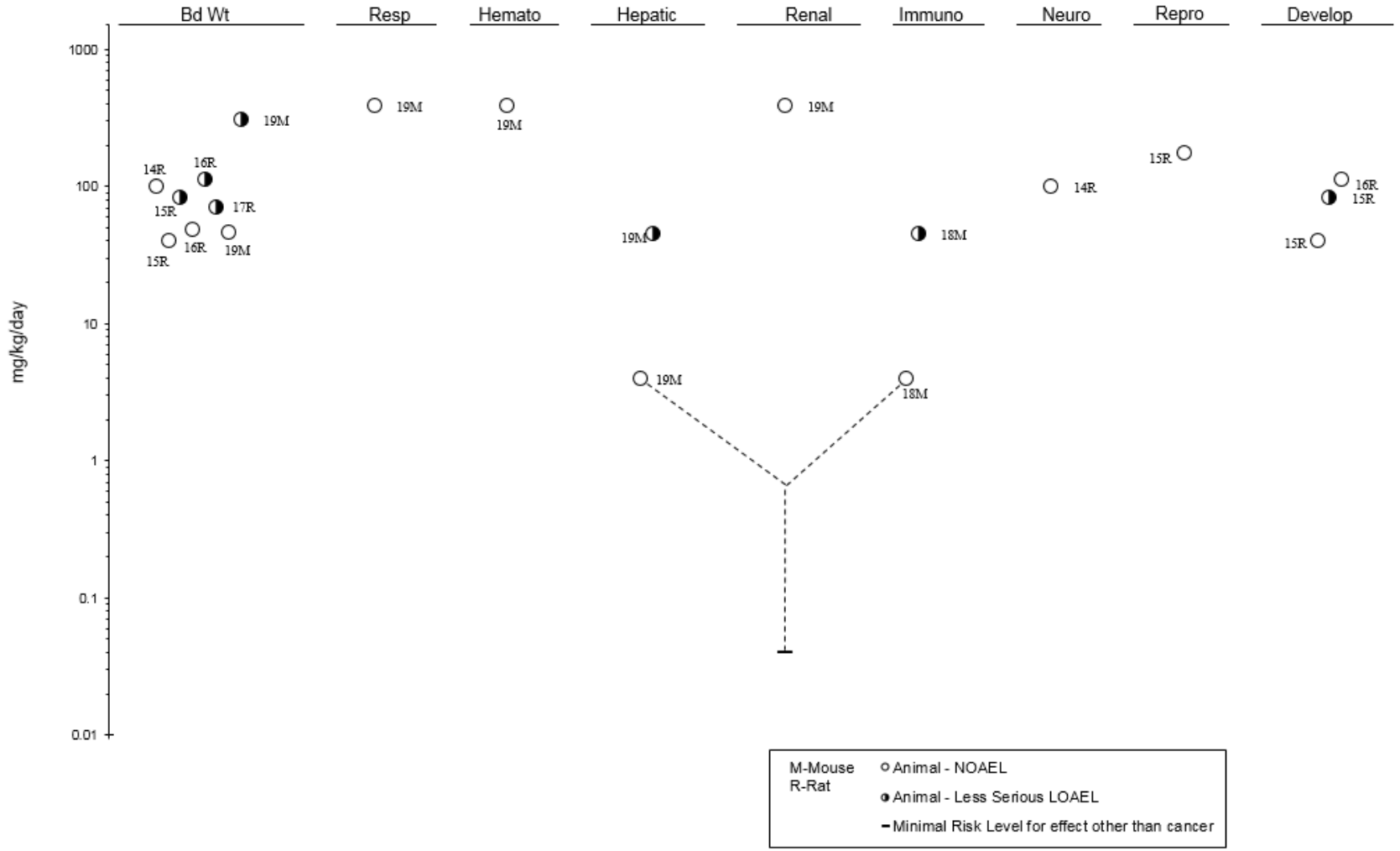


Figure 2-3. Levels of Significant Exposure to 1,1,2-Trichloroethane – Oral
Chronic (≥365 days)

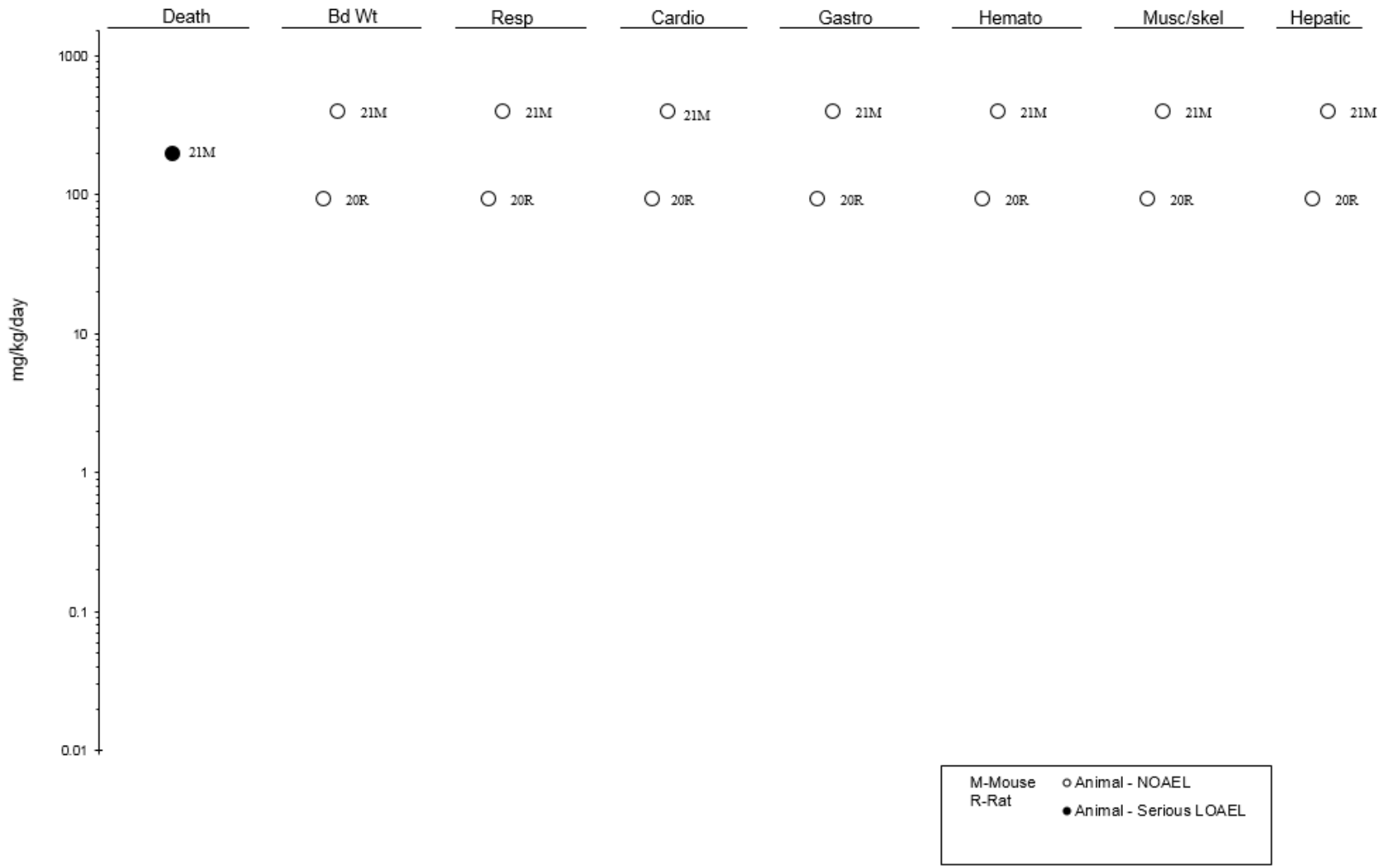


Figure 2-3. Levels of Significant Exposure to 1,1,2-Trichloroethane – Oral
Chronic (≥365 days)

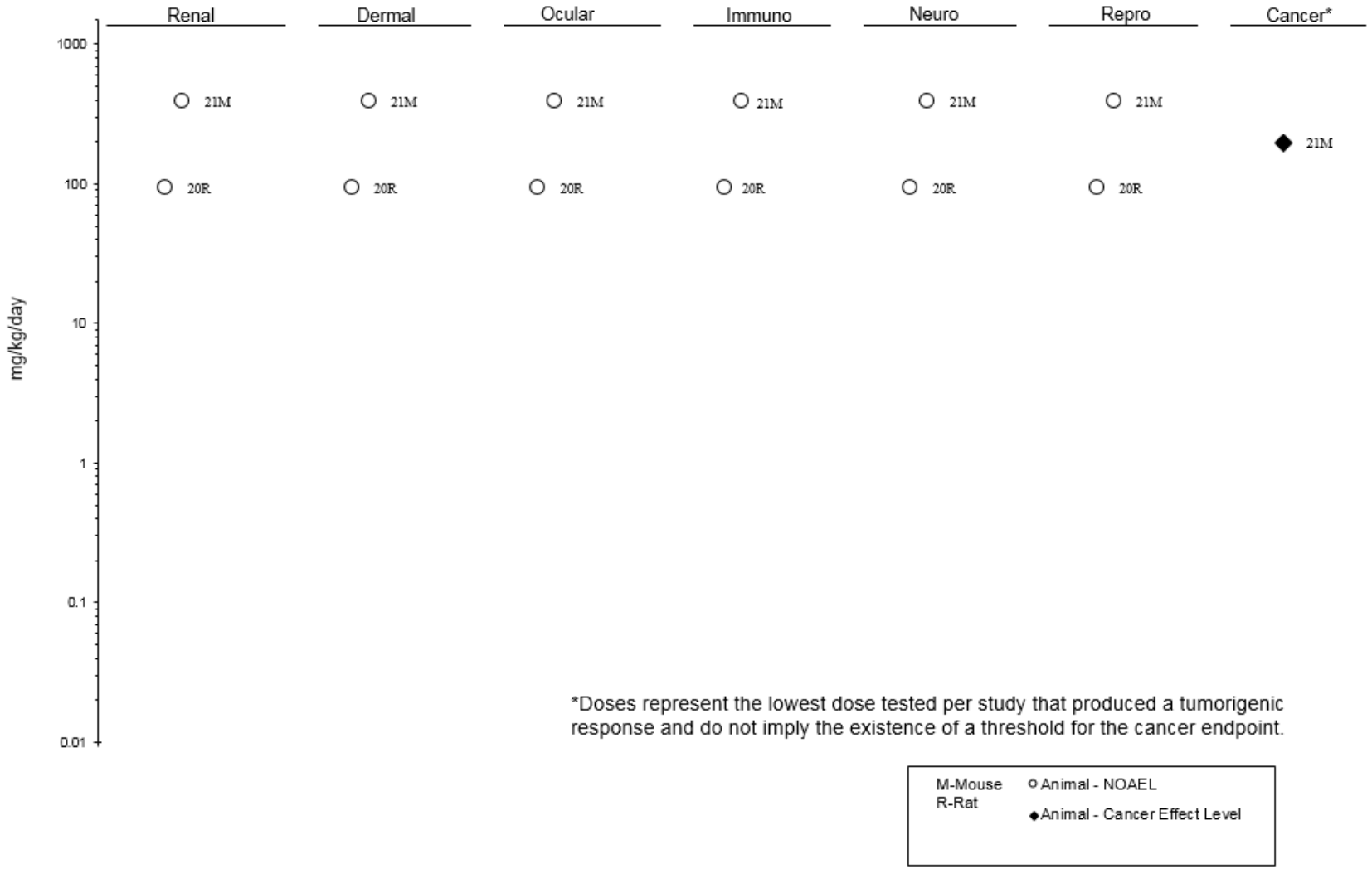


Table 2-3. Levels of Significant Exposure to 1,1,2-Trichloroethane – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effect
ACUTE EXPOSURE								
Human 1 M	5 minutes	698 mg/m^2	CS	Dermal		698		Stinging pain
Wahlberg 1984a								
Human 1 M	5 minutes	0.1 mL	CS	Dermal	0.1			
Wahlberg 1984a								
Rabbit (NS) 4 M	1 time	NR (mL/kg)	CS	Death			3.73	LD_{50}
Smyth et al. 1969								
Rabbit (NS) 5 NS	24 hours	0.01 mL	CS	Dermal	0.01			
Smyth et al. 1969								
Rabbit (NS) 4 NS	10 days 1 time/day	0.1 mL	CS	Dermal		0.1		Irritation
Wahlberg 1984b								
Guinea pig (NS) 6 NS	10 days 1 time/day	0.1 mL	CS	Dermal		0.1		Irritation
Wahlberg 1984b								
Guinea pig (NS) 11 M, F	12 hours	465 mg/cm^2	HP	Renal Dermal Neuro	465 465	 465 	 	 Skin damage No histological alterations
Kronevi et al. 1977								

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

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effect
Guinea pig (NS) 20 M, F	5–7 days	0, 116, 233, 931 mg/m^2	BW, CS	Death			116	5/20 dead
Wahlberg 1976								
INTERMEDIATE EXPOSURE								
Human 1 M	15 days 1 time/day	0.1 mL		Dermal	0.1			
Wahlberg 1984a								

BW = body weight; CS = clinical signs; d = day(s) F = female(s); HP = histopathology; LD_{50} = mortality; 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male(s); NOAEL = no-observed-adverse-effect level; NR = not reported; NS = not specified

2.2 DEATH

No studies were located regarding death in humans following exposure to 1,1,2-trichloroethane.

Mortality produced by inhalation of 1,1,2-trichloroethane has been studied in animals. Three of five rats exposed to 2,080 ppm of 1,1,2-trichloroethane for 2 hours died within about 24 hours, but five rats exposed to 890 ppm for 2 hours survived (Carlson 1973). Carpenter et al. (1949) reported that 2–4/6 rats died within 14 days following exposure to 2,000 ppm and 0–1/6 rats died following exposure to 1,000 ppm. The exact number of rats that died in each treatment group was not reported. In two experiments, 3/5 females exposed to 1,1,2-trichloroethane at 840 ppm and 3/5 females exposed to 1,527 ppm for 4 hours died; males treated at 1,474 and 1,527 ppm survived until study termination (Kirkpatrick 2001). The LC_{50} of 1,1,2-trichloroethane in rats exposed for 6 hours was 1,654 ppm (Bonnet et al. 1980). During exposure, animals were first excited and then somnolent. Most mortality occurred within 24 hours of exposure, but some deaths were reported up to 8 days later. No macroscopic lesions in the lungs, liver, or kidneys were found at autopsy. In rats exposed to 1,1,2-trichloroethane for 8 hours, the LC_{50} was 999 ppm (Pozzani et al. 1959). These authors reported, in a later study, that exposure to 500 ppm for 8 hours produced death in four out of six rats within 14 days (Smyth et al. 1969).

In mice, 12,934 ppm of 1,1,2-trichloroethane was found to be the minimum lethal concentration in a 2-hour exposure test (Lazarew 1929). The animals laid down on their sides and lost control of their reflexes prior to death. An LC_{50} value of 416 ppm was calculated in mice exposed for 6 hours and observed for 14 days (Gradiski et al. 1978). In mice exposed to 3,750 ppm of 1,1,2-trichloroethane, the LT_{50}, or exposure duration that produced mortality in one-half of the mice tested, was calculated to be 600 minutes (Gehring 1968).

No exposure-related effects on mortality were observed in Fischer 344 CDF Crl:BR rats exposed whole-body to 1,1,2-trichloroethane at up to 100 ppm 6 hours/day, 5 days/week for 13 weeks (Kirkpatrick 2002).

Several reports indicate that 1,1,2-trichloroethane may be lethal to animals following oral exposure. An LD_{50} of 837 mg/kg was calculated for gavage-administered, undiluted 1,1,2-trichloroethane in female rats (Smyth et al. 1956, 1969). Moody et al. (1981) reported no mortality among fasted rats given single oral doses of 1,1,2-trichloroethane in mineral oil at 1,080 mg/kg; however, only deaths during the first 18 hours after administration were recorded, and only three rats were tested. In mice, the oral LD_{50} of

1,1,2-trichloroethane administered by gavage in water was reported to be 378 mg/kg for males and 491 mg/kg for females (White et al. 1985). Necropsy of mice that died in this study revealed hemorrhagic areas in the lungs and pale coloration of the liver, which may also have been caused by hemorrhage. These effects may have contributed to the death of these animals. The only dog given 1,1,2-trichloroethane (vehicle not specified) at 722 mg/kg died, but all five that received doses ranging from 144 to 433 mg/kg survived (Wright and Schaffer 1932).

Lethality was also investigated in two short-term, repeated-dose studies. Oral doses of 1,1,2-trichloroethane given by gavage in water at 300 mg/kg for 7 days resulted in the death of all seven mice tested (Kallman et al. 1983). Doses up to 100 mg/kg/day did not produce death in this study. Oral administration by gavage of 38 mg/kg/day in 10% Emulphor for 14 days did not produce mortality in mice (White et al. 1985).

One long-term study investigated the effect of 1,1,2-trichloroethane on animal survival. A large number of the deaths occurred in female mice administered 195 mg/kg 5 days/week for 78 weeks; the deaths occurred early in the experiment, were not tumor-related, and did not appear to have a common cause (NCI 1978). No deaths were observed in male mice. In rats, survival was not affected by oral administration of doses of 1,1,2-trichloroethane as high as 92 mg/kg for 78 weeks (NCI 1978). However, rat vehicle controls had unusually high mortality in this study.

Dermally applied 1,1,2-trichloroethane has been reported to cause death in animals. A single dermal application of 116 mg/cm^2 (0.25 mL applied to a 3.1-cm^2 area of the back) was allowed to remain on the skin of guinea pigs until it disappeared (5–7 days). This treatment resulted in the death of 25% of the guinea pigs tested within 28 days (Wahlberg 1976). Doses of 233 and 931 mg/cm^2 killed all tested animals within 3 days in this study.

2.3 BODY WEIGHT

No studies were located regarding body weight effects in humans following exposure to 1,1,2-trichloroethane.

No alterations in body weight gain were observed in rats exposed to up to 100 ppm 1,1,2-trichlorothane by inhalation for 13 weeks (Kirkpatrick 2002).

Alterations in body weight gain were observed in several oral exposure studies. Male rats administered a single gavage dose of 1,1,2-trichloroethane (in 10 mL/kg corn oil) at 200 mg/kg showed decreased body weight gain (27% lower than controls on days 0–7), whereas body weights were unaffected in females (Beck 2004). Rats given 180 mg/kg/day in liquid paraffin for 7 days grew only 8% over the course of the experiment, whereas control rats grew 34% (Platt and Cockrill 1969). In mice, body weight gain was not significantly affected by gavage administration of 1,1,2-trichloroethane in 10% Emulphor at 38 mg/kg/day for 14 days (White et al. 1985).

In intermediate-duration studies, body weight gain was decreased approximately 60% in rats given 69 mg/kg/day by gavage in corn oil for 7 weeks (Story et al. 1986). In rats administered 1,1,2-trichloroethane at up to 98 mg/kg/day in drinking water for 13 weeks, the body weights of treated males were 3–7% higher than controls, and females treated at the highest dose showed only a nonsignificant reduction in body weights (4% lower than controls) at study termination; these effects were not considered treatment-related (Maurissen et al. 2005). However, decreased body weight gain was reported in P1 and F1 female rats exposed to 1,1,2-trichloroethane in drinking water at 82 mg/kg/day for two generations (Mylchreest 2006) and rats exposed to 1,1,2-trichloroethane in drinking water at 111 mg/kg/day on gestation days (GDs) 6–20 (Wilson 2005). Kallman and Kaempf (1984) reported that body growth in male mice was unchanged by 90-day exposure to 46 mg/kg/day in the drinking water. In a second study, exposure to 1,1,2-trichloroethane in the drinking water for 90 days produced a dose-related inverse response in male mice that was significant at 305 mg/kg/day (White et al. 1985). Weight gain in female mice was not affected in this study.

When administered by gavage in corn oil, doses of 92 mg/kg/day in rats and 390 mg/kg/day in mice for 78 weeks (NCI 1978) did not inhibit body growth.

2.4 RESPIRATORY

No studies were located regarding respiratory effects in humans following exposure to 1,1,2-trichloroethane.

Several studies investigated the respiratory effects of acute 1,1,2-trichloroethane inhalation in animals. In two studies conducted by Kirkpatrick (2001), rats were exposed to 1,1,2-trichloroethane for 4 hours. Increased protein content of bronchoalveolar lavage fluid was observed in male rats exposed to 1,473 ppm and in female rats exposed to 840 ppm. Rats exposed to ≥58 ppm showed necrosis of the

olfactory epithelium (at nasal levels III, IV, and V); the incidence and severity of these lesions increased in an exposure-related manner. No gross alterations of respiratory organs and tissues were observed in rats that survived a 6-hour exposure test from which an LC_{50} of 1,654 ppm was calculated (Bonnet et al. (1980).

In an intermediate-duration study, no significant changes in absolute or relative lung weights were observed in Fischer 344 CDF Crl:BR rats exposed whole-body to 1,1,2-trichloroethane at up to 100 ppm 6 hours/day, 5 days/week for 13 weeks. However, nasal lesions of the olfactory epithelium of the nasal turbinates (including vacuolization and microcyst formation, respiratory epithelial metaplasia, and/or atrophy) were observed at 40 and 100 ppm (Kirkpatrick 2002). The mechanisms involved in 1,1,2-trichloroethane-mediated respiratory toxicity are not known.

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

Respiratory effects have been studied in orally exposed animals. No alterations in absolute or relative lung weights were observed in mice administered 38 mg/kg/day 1,1,2-trichloroethane by gavage for 14 days (White et al. 1985) or 305 mg/kg/day (males) or 384 mg/kg/day (females) in the drinking water for 90 days (White et al. 1985). These dose levels were considered NOAEL values (in the absence of evaluations of respiratory function) based on biomedical judgement. Histopathological examination of respiratory organs and tissues (lungs, bronchi, and trachea) found no increase in the occurrence of non-neoplastic lesions following 78 weeks of oral 1,1,2-trichloroethane administration in corn oil at doses of 46 or 92 mg/kg/day in rats and 195 or 390 mg/kg/day in mice (NCI 1978).

2.5 CARDIOVASCULAR

No studies were located regarding cardiovascular effects in humans following exposure to 1,1,2-trichloroethane.

There are limited data in animals on the potential cardiotoxicity of 1,1,2-trichloroethane. No histological alterations were observed in rats exposed to 100 ppm 6 hours/day, 5 days/week for 13 weeks (Kirkpatrick 2002), in rats administered via gavage 92 mg/kg 5 days/week for 78 weeks (NCI 1978), or in mice receiving gavage doses of 390 mg/kg 5 days/week for 78 weeks (NCI 1978).

2.6 GASTROINTESTINAL

No studies were located regarding gastrointestinal effects in humans following exposure to 1,1,2-trichloroethane.

No histopathological alterations were observed in gastrointestinal organs and tissues from rats following 13 weeks of inhalation exposure to 1,1,2-trichloroethane at up to 100 ppm (Kirkpatrick 2002). In contrast, there is some evidence for adverse gastrointestinal effects in animals following oral exposure. Mice that died following administration by gavage of single oral doses of 1,1,2-trichloroethane >200 mg/kg displayed a dose-related increase in the incidence of gastric irritation (White et al. 1985). Mild inflammation and congestion of the gastrointestinal tract, as well as nausea, were noted in a dog given oral administration of 144 mg/kg (Wright and Schaffer 1932). Severe irritation and hemorrhage were found in two of the three dogs given doses of 433 or 722 mg/kg. In chronic exposure studies, histopathological examination of gastrointestinal organs and tissues revealed no increase in the occurrence of non-neoplastic lesions following 78 weeks of oral 1,1,2-trichloroethane administration by gavage (5 days/week) at doses of 92 mg/kg in rats and 390 mg/kg in mice (NCI 1978).

2.7 HEMATOLOGICAL

No studies were located regarding hematological effects in humans following exposure to 1,1,2-trichloroethane.

In the one study identified that examined hematological effects in animals following inhalation exposure to 1,1,2-trichloroethane, no significant effects on a comprehensive set of hematological parameters were observed in rats exposed to up to 100 ppm 6 hours/day, 5 days/week for 13 weeks (Kirkpatrick 2002).

Hematological effects (total and differential blood cell counts and coagulation parameters) were the subject of several oral studies in animals. No hematological effects were found after daily administration to mice of 1,1,2-trichloroethane by gavage at 38 mg/kg for 14 days (White et al. 1985). No hematological effects were found in male mice exposed to ≤305 mg/kg/day in drinking water for 90 days, but changes in hematological parameters were recorded in females that received doses as low as 3.9 mg/kg/day (White et al. 1985). These included mild decreases in hematocrit and hemoglobin at 384 mg/kg/day; increases in platelets and fibrinogen were found in all groups (≥3.9 mg/kg/day), but were not dose-related. In the 384 mg/kg/day group, leukocytes were elevated, compared to controls, and only slightly higher than the historical control value in this laboratory. There was also a decrease in prothrombin time that appeared to

be dose-related and became statistically significant at 44 mg/kg/day in female mice. The biological significance of the small magnitude of changes is unclear, particularly for humans because test results vary widely between species. Additionally, hepatic effects, which occurred in test subjects at low concentrations, may influence prothrombin time; therefore, the highest dose of 384 mg/kg/day was considered a NOAEL.

Histopathological examination of spleen and bone marrow found no increase in the occurrence of non-neoplastic lesions following 78 weeks of oral 1,1,2-trichloroethane administration of 92 mg/kg/day in rats and 390 mg/kg/day in mice (NCI 1978).

2.8 MUSCULOSKELETAL

No studies were located regarding musculoskeletal effects in humans following exposure to 1,1,2-trichloroethane.

Studies in animals have not found histological alterations in bone or skeletal muscle in rats exposed up to 100 ppm 6 hours/day, 5 days/week for 13 weeks (Kirkpatrick 2002) or in rats and mice administered via gavage up to 92 or 390 mg/kg, respectively, for 78 weeks (NCI 1978).

2.9 HEPATIC

No studies were located regarding hepatic effects in humans following exposure to 1,1,2-trichloroethane.

Several studies examined the hepatotoxicity of inhaled 1,1,2-trichloroethane vapor in animals. In rats, inhalation of 2,080 ppm of 1,1,2-trichloroethane for 2 hours resulted in a small, but significant, increase in ALT levels measured 22 hours after exposure ended (Carlson 1973). This treatment did not affect AST, glucose-6-phosphatase, or liver weight. Macroscopic examination of rats that survived (number not specified) exposure to 250 ppm of 1,1,2-trichloroethane for 4 hours and 250–500 ppm for 7 hours revealed necrosis and tissue damage in the liver (Unpublished data, Dow Chemical Co., cited in Torkelson and Rowe 1981). Hepatocellular necrosis was also noted in rats exposed to 1,1,2-trichloroethane at ≥181 ppm for 4 hours; clinical chemistry parameters of liver function were not evaluated and liver weights were not affected (Kirkpatrick 2001). Mice exposed to 800 ppm of 1,1,2-trichloroethane for 3 hours had decreased adenosine triphosphate (ATP), increased liver triglycerides, decreased plasma triglycerides, and increased ALT (Takahara 1986c). Recovery occurred within 20 hours for all parameters except ALT, which remained elevated. The ET_{50} (duration of exposure that produced

increased ALT levels in one-half of the exposed mice) for increased ALT levels in mice exposed to 3,750 ppm of 1,1,2-trichloroethane was 17.5 minutes (Gehring 1968).

Minor fatty changes and cloudy swelling were found in the livers of female rats exposed to 30 ppm of 1,1,2-trichloroethane for 16 days (Unpublished data, Dow Chemical Co., cited in Torkelson and Rowe 1981). Rats exposed to 1,1,2-trichloroethane 6 hours/day, 5 days/week for 13 weeks showed increased cholesterol at 100 ppm (males) or 40 ppm and 100 ppm (females); this effect was not strictly dose-related. Rats of both sexes exposed to 100 ppm showed increased incidences of hepatocellular vacuolization (minimal in severity). The study authors suggested that while this effect was probably degenerative, the lesions did not progress to centrilobular hepatocellular necrosis (Kirkpatrick 2002). The toxicological significance of increased cholesterol is unclear in the absence of effects on ALT or AST or liver weights. Six months of exposure up to 15 ppm 1,1,2-trichloroethane did not have histopathological effects on the liver in rats, guinea pigs, or rabbits (Unpublished data, Dow Chemical Co., cited in Torkelson and Rowe 1981).

Numerous studies examined hepatic effects in animals following oral exposure to 1,1,2-trichloroethane. Rats administered a single gavage dose of 1,1,2-trichloroethane at 667 mg/kg/day and sacrificed 6–72 hours after treatment showed significantly increased levels of ALT, sorbitol dehydrogenase, and glutamate dehydrogenase in the serum (Xia and Yu 1992). Tyson et al. (1983) found significant increases in AST and ALT following one-time gavage administration of 1,1,2-trichloroethane at about 92 mg/kg/day to rats (based on data obtained using GrabIt! Software). The NOAEL for this effect was about 46 mg/kg/day; the ED_{50} (the dose that produced an elevation in enzyme levels above the normal range in 50% of the test animals) was 60 mg/kg. Biochemical changes, characterized by decreased cytochrome P-450 and ALA-dehydratase, and changes in microsomal fatty acid content occurred after administration of 1,080 mg/kg by gavage in rats (Moody and Smuckler 1986; Moody et al. 1981); the toxicological significance of these effects is unclear. Increased relative liver weight was also seen in this study, which was limited by small sample size (Moody et al. 1981). Glucose-6-phosphate dehydrogenase levels increased 195% and NADH2-cytochrome c reductase levels decreased 33%, in rats administered 1,1,2-trichloroethane orally in liquid paraffin at 180 mg/kg/day for 7 days (Platt and Cockrill 1969). Liver weight (relative) and other liver biochemical endpoints were not significantly changed in this study. The toxicological significance of these biochemical changes (in the absence of effects on other liver endpoints) is unclear. Necropsy of mice that died following single oral doses of 1,1,2-trichloroethane by gavage in water at 200–600 mg/kg revealed pale coloration of the liver (White et al. 1985). Dogs given a single dose of ≥144 mg/kg 1,1,2-trichloroethane had congestion, fatty degeneration, edema, and the onset

of necrosis in the liver (Wright and Schaffer 1932). Extensive liver necrosis occurred in one of the three dogs given ≥433 mg/kg. ALT levels were not affected by 14-day administration of 1,1,2-trichloroethane by gavage at 38 mg/kg/day in mice (White et al. 1985).

In male mice exposed to 1,1,2-trichloroethane for 90 days in the drinking water, liver glutathione decreased 16% following exposure to 46 mg/kg/day and 28% following exposure to 305 mg/kg/day; serum aminotransferase levels were not significantly increased at either dose (White et al. 1985). In the same study, female mice that received 384 mg/kg/day had a 13% increase in liver glutathione and significantly elevated ALT levels. Liver weight was also significantly increased in females treated at 384 mg/kg/day (32% higher than controls based on absolute weight and 26% higher than controls based on relative weight). AST levels were increased in females exposed to ≥3.9 mg/kg/day, but this was not considered to be a compound-related effect because no dose-relationship was established. Females treated at 44 and 384 mg/kg/day showed minimal effects on microsomal activity (decreased cytochrome P-450 and decreased aniline hydroxylase activity). The NOAEL for liver effects in this study was considered 3.9 mg/kg/day, based on evidence of mild liver toxicity at 384 mg/kg/day. No increase in the occurrence of non-neoplastic lesions in the liver was found in histopathological examinations following 78 weeks of oral 1,1,2-trichloroethane administration by gavage in corn oil at doses of 92 mg/kg/day in rats and 390 mg/kg/day in mice (NCI 1978).

One study investigated the hepatotoxicity of dermally applied 1,1,2-trichloroethane in animals. Guinea pig liver glycogen content was reduced within 2 hours following dermal application of 1 mL of 1,1,2-trichloroethane to a 3.1 cm^2 area of the back (465 mg/cm^2) (Kronevi et al. 1977). Hydropic changes in the liver were also found. These effects may not have been compound-related, however, since they were found in animals killed under anesthesia produced by pentobarbital, but not unanesthetized animals. Untreated controls were not used in this study. The authors suggested that these liver effects may have been due to an interaction between 1,1,2-trichloroethane and pentobarbital. This possibility is discussed further in Section 3.4.

In male mice administered 1,1,2-trichloroethane via a single intraperitoneal injection, the reported ED_{50} values for increased serum ALT were approximately 144 mg/kg (based on the ED_{50} reported in mL/kg) and 240 mg/kg (based on the ED_{50} reported in mmol/kg) (Klaassen and Plaa 1966).

Although the mechanisms of action associated with 1,1,2-trichloroethane-mediated hepatotoxicity are largely unknown, limited data suggest that free radicals and aryl chlorides (including chloroacetic acid)

generated from the metabolism of 1,1,2-trichloroethane and DNA adduct formation may play a role (Mazzullo et al. 1986; Tyson et al. 1983). One study showed that 1,1,2-trichloroethane tested positive for DNA adduct formation in rat and mouse liver (Mazzullo et al. 1986).

2.10 RENAL

No studies were located regarding renal effects in humans following exposure to 1,1,2-trichloroethane.

The renal effects of 1,1,2-trichloroethane have been studied in animals following inhalation exposure. In the rat, inhalation of 250 ppm of 1,1,2-trichloroethane for 4 hours produced kidney necrosis. Exposure to 250 or 500 ppm for 7 hours produced marked kidney damage (Unpublished data, Dow Chemical Co., cited in Torkelson and Rowe 1981). No macroscopic lesions were found in the kidneys of rats that survived a 6-hour exposure test from which an LC_{50} of 1,654 ppm was calculated (Bonnet et al. 1980). No alterations in kidney weight (absolute or relative) or histopathology were observed in rats exposed to up to 100 ppm 1,1,2-trichloroethane 6 hours/day, 5 days/week for 13 weeks; additionally, there were no significant effects on serum chemistry parameters indicative of kidney function (Kirkpatrick 2002). Similarly, no renal histopathological effects were observed in rats, guinea pigs, or rabbits exposed to 15 ppm of 1,1,2-trichloroethane for 6 months (Unpublished data, Dow Chemical Co., cited in Torkelson and Rowe 1981).

There are some reports of renal toxicity in animals after oral exposure to 1,1,2-trichloroethane, although most studies did not report significant findings. Cloudy swelling and congestion of the kidney were found by histopathological examination in dogs given 1,1,2-trichloroethane orally at ≥144 mg/kg (Wright and Schaffer 1932). There was a significant, low-level depression of *in vitro* organic ion uptake in renal cortical slices taken from rats given single gavage doses of 1,1,2-trichloroethane at 72–505 mg/kg (Watrous and Plaa 1972a), although there was no clear dose response. In mice administered 1,1,2-trichloroethane at up to 2,886 mg/kg, the renal toxicity results were inconsistent, with varying positive and inverse dose-response relationships in different trials (Watrous and Plaa 1972a). There were no significant changes in absolute or relative kidney weight or blood urea nitrogen in mice given 1,1,2-trichloroethane by gavage for 14 days at a dose of 38 mg/kg/day or in the drinking water for 90 days at a dose of 305 mg/kg/day in males and 384 mg/kg/day in females (White et al. 1985). No increase in the occurrence of non-neoplastic lesions was found in the kidney histopathological examination following 78 weeks of oral 1,1,2-trichloroethane administration in corn oil at doses of 92 mg/kg/day in rats and 390 mg/kg/day in mice (NCI 1978).

The renal effects of dermally applied 1,1,2-trichloroethane in animals were examined in one study. No histopathological changes were found in the kidneys of guinea pigs 2, 6, or 12 hours after dermal application of 1,1,2-trichloroethane at 465 mg/cm^2 (Kronevi et al. 1977).

2.11 DERMAL

No studies were located regarding dermal effects in humans following inhalation or oral exposure to 1,1,2-trichloroethane.

No histological skin alterations were observed in animals following inhalation exposure of rats to up to 100 ppm 6 hours/day, 5 days/week for 13 weeks (Kirkpatrick 2002) or in rats or mice administered via gavage 92 or 390 mg/kg, respectively, 5 days/week for 78 weeks (NCI 1978).

Several studies have evaluated the dermal toxicity of 1,1,2-trichloroethane in humans. A subject dermally exposed to 698 mg/cm^2 (1.5 mL on 3.1 cm^2 of the forearm) 1,1,2-trichloroethane under occlusion for 5 minutes reported stinging and burning sensations and displayed transient whitening of the skin (Wahlberg 1984a). A small, immediate increase in blood flow was measured by laser Doppler flowmetry, but no visible erythema was present. In an open test on the same subject, in which 0.1 mL of 1,1,2-trichloroethane was applied to the skin without a cover disc, there was no effect on blood flow and no visible erythema was found (Wahlberg 1984a). A volunteer given daily open application of 0.1 mL of 1,1,2-trichloroethane for 15 days did not have any visible skin reactions, nor was there any increase in skin-fold thickness, which was measured using calipers (Wahlberg 1984b).

The dermal effects of 1,1,2-trichloroethane have also been studied in animals. Dermal application of 1,1,2-trichloroethane at 465 mg/cm^2 produced pyknotic nuclei in epidermal cells within 15 minutes in guinea pigs (Kronevi et al. 1977). As the duration of exposure increased, damage progressed to vesicle formation and separation of skin layers (Kronevi et al. 1977). Rabbits given a single application of 0.01 mL of 1,1,2-trichloroethane had no effects other than slight capillary congestion (Smyth et al. 1969). Duprat et al. (1976) compared the dermal irritancy of chlorinated aliphatic solvents in rabbits and determined that 1,1,2-trichloroethane (concentration not reported) was a severe skin irritant compared to other compounds in this group, producing serious erythema, serious edema, and necrosis. In a repeated-dose study, daily open application of 0.1 mL for 10 days increased skin-fold thickness 170% in guinea

pigs and 218% in rabbits (Wahlberg 1984b). All animals in this study displayed marked erythema and edema, and fissuring and scaling were also seen.

2.12 OCULAR

No studies were located regarding ocular effects in humans following exposure to 1,1,2-trichloroethane.

No exposure-related ocular effects, as evaluated by an ophthalmologic examination, were observed in rats after inhalation exposure to 1,1,2-trichloroethane up to 100 ppm 6 hours/day, 5 days/week for 13 weeks (Kirkpatrick 2002). Similarly, histopathological examination of the eye found no increase in the occurrence of non-neoplastic lesions following 78 weeks of oral 1,1,2-trichloroethane administration at doses of 92 mg/kg in rats and 390 mg/kg in mice (NCI 1978). 1,1,2-Trichloroethane (presumably neat, but not explicitly specified in the study report) applied directly to the eye did not produce significant cornea1 necrosis in rabbits (Smyth et al. 1969). It was classified as a slight eye irritant by Duprat et al. (1976), who found moderate catarrhal conjunctivitis and epithelial abrasion following application in rabbits. Neither study reported the dose of 1,1,2-trichloroethane applied.

2.13 ENDOCRINE

No studies were located regarding non-neoplastic endocrine effects in humans or animals following exposure to 1,1,2-trichloroethane. 1,1,2-Trichloroethane induced increased incidences of adrenal pheochromocytomas (not specified as benign or malignant) in mice after exposure for 78 weeks (NCI 1978).

2.14 IMMUNOLOGICAL

No studies were located regarding immunological effects in humans following exposure to 1,1,2-trichloroethane.

Immunological effects in mice orally exposed to 1,1,2-trichloroethane were studied by Sanders and co-workers (Sanders et al. 1985; White et al. 1985). Gavage administration of up to 38 mg/kg/day for 14 days had no effect on humoral or cell-mediated immune response to sRBCs in male mice (Sanders et al. 1985). Humoral immune response was measured by the number of IgM antibody forming cells (AFCs) produced against sRBCs in the spleen. Spleen and thymus weight (absolute or relative) were not

affected by treatment (White et al. 1985). In a longer-term study, mice were exposed to 1,1,2-trichloroethane in the drinking water for 90 days (Sanders et al. 1985, White et al. 1985). Humoral immune response was measured by the number of spleen AFCs produced in response to sRBCs, hemagglutination titers, and spleen lymphocyte response to B-cell and T-cell mitogens (Sanders et al. 1985). The number of spleen AFCs to sRBC (reported as ratio of AFC/spleen weight and AFC/per 10^6 spleen cells) was not consistently affected by treatment. A significant increase was obtained in females that received 384 mg/kg/day, on day 4 following immunization and no effect was observed on an AFC/spleen basis. Significant increases for the AFC/10^6 cell ratio were detected in males treated at 4.4 and 46 mg/kg/day, while the AFC/total spleen ratio was significantly increased at 46 mg/kg/day; neither outcome was affected in males treated at 305 mg/kg/day. The response of splenic lymphocytes to mitogens was unaffected by treatment. Hemagglutination titers (expressed as $\log_2$ titers) exhibited an inverse dose-related depression that was significant starting at 44 mg/kg/day in females and 46 mg/kg/day in males. Based on the transformation of $\log_2$ titers to antibody dilutions, hemagglutination levels were decreased 47 and 59% in males treated at 46 and 305 mg/kg/day, respectively, and 40 and 45% in females treated at 3.9 and 384 mg/kg/day, respectively. Both delayed-type hypersensitivity and popliteal lymph node proliferation responses were examined in the 90-day study. Peritoneal macrophages from males exposed to 305 mg/kg/day had a significantly depressed ability to phagocytize sRBCs; this effect was not found in females. Changes in the activity of fixed macrophages of the reticuloendothelial system to clear and distribute sRBCs (observed in females only) were not considered treatment-related owing to variations in the direction and magnitude of effects. Spleen weight (absolute or relative) was unchanged in most groups, but was increased in females exposed to 384 mg/kg/day (White et al. 1985). Thymus weight (absolute or relative) was not affected in any group. On the basis of this study, 44 mg/kg/day was chosen as the LOAEL based on decreased hemagglutination titers; 3.9 mg/kg/day was considered the NOAEL. The mechanisms involved in 1,1,2- trichloroethane-mediated immunotoxicity are not known.

No increase in the occurrence of non-neoplastic lesions was found in the spleen, thymus, bone marrow, or lymph nodes following 78 weeks (5 days/week) of gavage 1,1,2-trichloroethane administration at doses of 92 mg/kg/day in rats and 390 mg/kg/day in mice (NCI 1978).

2.15 NEUROLOGICAL

No studies were located regarding neurological effects in humans following exposure to 1,1,2-trichloroethane.

Studies in animals indicate that inhalation of 1,1,2-trichloroethane may produce neurological effects. Rats exposed to 1,1,2-trichloroethane at about 350–1,720 ppm for up to 1 hour showed significant effects on the central vestibular system (namely slow-phase eye velocity [SPV] and the duration of nystagmus) following optokinetic, vestibular, and combined optokinetic and vestibular stimulation. The duration of nystagmus and the generation of saccades (quick reposition of the eyes) were unaffected by 1,1,2-trichloroethane exposure (Niklasson et al. 1993).This study was not used as the basis of a LOAEL because all data in the report were presented graphically (statistical significance based on simple regression analysis were provided in the text; pairwise-tests were not performed). Two studies by Kirkpatrick (2001) showed that exposure to 1,1,2-trichloroethane for 4 hours resulted in sleepiness and decreased respiration in male rats at ≥1,474 ppm and in female rats at ≥840 ppm. Exposure to 1,654 ppm of 1,1,2-trichloroethane for 6 hours produced excitation, followed by sleepiness, in rats (Bonnet et al. 1980). Mice exposed to 1,1,2-trichloroethane vapor for 2 hours laid down on their sides at 1,833 ppm and lost control of their reflexes at 2,749 ppm. These concentrations are substantially lower than the minimum lethal concentration of 12,934 ppm that was reported in this study, which suggests that 1,1,2-trichloroethane exhibits increased central nervous system depression (Lazarew 1929). The ET_{50} for anesthesia (duration of exposure that produced anesthesia in one-half of the exposed mice) in mice exposed to 3,750 ppm was 18 minutes (Gehring 1968). This was substantially shorter than the LT_{50} of 600 minutes for lethality, indicating increasing central nervous system depressant potency. A 50% elevation in the threshold for pentylenetetrazol-induced seizures of central nervous system function occurred in mice after exposure to 418 ppm of 1,1,2-trichloroethane for 4 hours (De Ceaurriz et al. 1981). This effect may indicate depression of central nervous system function. The mechanisms involved in 1,1,2-trichloroethane-mediated neurotoxicity are not known.

Neurological effects have also been reported in oral exposure studies, particularly via gavage administration of 1,1,2-trichloroethane. Rats administered a single gavage dose of 1,1,2-trichloroethane (in 10 mL/kg corn oil) at 200 mg/kg showed an increased incidence of slight (but definite) gait impairment on study day 0 (4/12 males and 5/12 females; 0/12 controls). Motor activity counts were significantly altered at ≥55 mg/kg for some testing intervals; however, these changes were not consistently dose- or duration-related. There were no statistically significant effects on mean total or ambulatory motor activity counts on study days 0, 7, or 14. Brain weight (absolute) and microscopic examinations of the nervous tissues did not show treatment-related effects (Beck 2004). All mice given single gavage doses of 1,1,2-trichloroethane at ≥450 mg/kg were sedated within 1 hour of administration (White et al. 1985). The ED_{50} for motor impairment (the dose that produced motor impairment in one-half of the test animals) in mice was 128 mg/kg, with the peak effect occurring within 5 minutes of

exposure to a single dose (Borzelleca 1983). In dogs, single doses of 1,1,2-trichloroethane at 289–722 mg/kg produced drowsiness, incoordination, and partial narcosis after 12–50 minutes (Wright and Schaffer 1932).

Kallman et al. (1983) reported that 1,1,2-trichloroethane administered by gavage for 7 days produced a significant dose-related taste aversion to saccharin in the drinking water at 100 mg/kg, but not at ≤30 mg/kg. An ED_{50} of 32 mg/kg was calculated. Mice did not display a taste aversion to 1,1,2-trichloroethane itself when 46 mg/kg/day was added to the drinking water for 4 days (Kallman and Kaempf 1984). The mechanisms involved in 1,1,2-trichloroethane-mediated neurotoxicity are not known.

Longer-term studies did not report neurological effects following oral administration of 1,1,2-trichloroethane. Gavage administration of 38 mg/kg/day for 14 days did not affect absolute or relative (to body weight) brain weight in mice (White et al. 1985). Mouse brain weight (absolute or relative to body weight) was also unaffected by exposure to 305 mg/kg/day (males) and 384 mg/kg/day (females) in the drinking water for 90 days (White et al. 1985). NOAEL values were not derived from these studies because brain weight alone is not an adequate endpoint to assess neurotoxicity. Rats administered 1,1,2-trichloroethane at up to 98 mg/kg/day in drinking water for 13 weeks showed no evidence of neurological effects, based on functional observational battery tests and light microscopic examinations of nervous system tissues (Maurissen et al. 2005). No effect on the occurrence of non-neoplastic lesions in nervous system organs and tissues was found by histopathological examination following 78 weeks of oral 1,1,2-trichloroethane administration at doses of 92 mg/kg/day in rats and 390 mg/kg/day in mice (NCI 1978).

One study of neurological effects in animals following dermal exposure was located. No histopathological changes were found in the brains of guinea pigs 2, 6, or 12 hours after dermal application of 1,1,2-trichloroethane at 465 mg/cm^2 (Kronevi et al. 1977).

2.16 REPRODUCTIVE

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

Studies of orally administered 1,1,2-trichloroethane did not report significant reproductive effects in animals. In a two-generation study (Mylchreest 2006), rats showed no significant effects on reproduction,

based on evaluations of mating, fertility, implantations, sperm and estrous parameters, and light microscopic examinations of the reproductive tissues. Seidenberg et al. (1986) found no effect on number of litters resorbed or average number of neonates per litter in mice following 5 days of oral administration of 350 mg/kg/day in corn oil on days 8–12 of gestation.

Testes weight (absolute or relative) in mice was not affected when 1,1,2-trichloroethane was administered by gavage for 14 days at a dose of 38 mg/kg/day (White et al. 1985). Exposure to ≥46 mg/kg/day in the drinking water for 90 days produced a significant increase in relative, but not absolute, testes weight in mice (White et al. 1985). NOAEL and LOAEL values were not derived from these studies, however, because testes weight alone may not be an adequate endpoint to assess reproductive toxicity. Also, changes in testes weight are not necessarily associated with reproductive dysfunction. No effect on the occurrence of non-neoplastic lesions in structures of the reproductive system was found following administration of 92 mg/kg in rats and 390 mg/kg in mice for 78 weeks (5 days/week) (NCI 1978).

2.17 DEVELOPMENTAL

One study was located regarding developmental effects in humans due to exposure to 1,1,2-trichloroethane. A case-control study examined the association between the proximity to industrial air releases of 14 chlorinated solvents (including 1,1,2-tricholoroethane) and birth defects (including neural tube, oral cleft, limb deficiency, and congenital heart defects). Exposure was estimated with metrics that accounted for the proximity of residences to industrial release sites and the amount of chemicals released annually. All risk estimates were adjusted for year of delivery and maternal age, education, race/ethnicity, and region of residence. Most associations were not significant. However, proximity of emissions to several chlorinated solvents (including 1,1,2-trichloroethane, carbon tetrachloride, chloroform, ethyl chloride, and 1,2,3-trichloropropane) were positively associated with neural tube defects; associations were also observed for a few solvents and other types of defects. With respect to 1,1,2-trichloroethane, positive associations were found between maternal residential proximity to 1,1,2-trichloroethane emissions and neural tube defects (odds ratio [OR] 1.56; 95% confidence interval [CI] 1.11–1.28), spina bifida (OR 1.94; 95% CI 1.32–2.84), and septal heart defects (albeit weak; OR 1.12; 95% CI 1.01–1.24), but not limb deficiencies (OR 0.91; 95% CI 0.56–1.46) (Brender et al. 2014). When exposure risk values were examined as quartiles, there was a significant inverse linear trend for spina bifida ($p=0.026$), significant positive linear trend for septal defects ($p=0.031$), and a marginally significant ($p=0.059$) non-monotonic trend for isolated cleft palate. Strengths of the study included the large size (allowing for stratification by age) and the ability to account for the recurrence of birth defects (a known risk factor). No additive or

multiplicative interactions between exposure and birth defects by maternal age were detected. Weaknesses of the study include: (1) no direct air measurements of chlorinated solvents; and (2) residential histories of mothers throughout pregnancy were not available. Since mothers were exposed to multiple chemicals, the observed effects cannot be attributed to 1,1,2-trichloroethane alone. In addition, Wikoff et al. (2018) suggest that proximity to exposure sources (as a proxy of exposure) is likely to introduce bias; the use of a continuous variable to quantify exposure rather than an undefined threshold distance would eliminate some of the bias. Despite the use of proximity to emissions as an exposure metric, Brender et al. (2014) showed a correlation between estimated exposures and air measurements from the Texas Commission of Environmental Quality.

Several studies of the developmental effects of 1,1,2-trichloroethane in animals were found. Female rats administered 1,1,2-trichloroethane at up to 111 mg/kg/day in drinking water on days 6–20 of gestation showed no effects on fetal weight, fetal sex distribution, or incidences of external, visceral, or skeletal abnormalities on GD 20 (Wilson 2005). In a 2-generation study in rats (Mylchreest 2006), F1 and F2 pups exposed to 1,1,2-trichloroethane at 82.2 mg/kg/day showed decreased body weights on postnatal days 4 to 21 (13–18% lower than controls). There were no significant effects on pup body weights at birth or on the timing of developmental milestones (vaginal opening or preputial separation). In pregnant female mice administered 350 mg/kg/day 1,1,2-trichloroethane via gavage on days 8–12 of gestation, the percent survival of neonates from day 1 through day 3 was not affected by treatment, and neither was average neonatal weight measured on days 1 and 3 postpartum (Seidenberg et al. 1986).

2.18 OTHER NONCANCER

No studies were located regarding other noncancer effects in humans or animals following exposure to 1,1,2-trichloroethane.

2.19 CANCER

One study was located regarding cancer in humans following inhalation exposure to 1,1,2-trichloroethane. A case-control study by Dosemeci et al. (1999) that investigated the risks of RCC caused by occupational exposures to solvents, chlorinated aliphatic hydrocarbons (CAHCs), and nine individual CAHCs (including 1,1,2-trichloroethane) failed to show an association between exposure to 1,1,2-trichloroethane and RCC, with ORs and 95% CIs for males and females of 0.90 (0.5–1.6) and 0.95 (0.2–4.4), respectively.

One study of cancer in animals orally exposed to 1,1,2-trichloroethane was located. There was no significant increase in the occurrence of neoplasms in male or female rats following 78 weeks (5 days/week) of gavage administration of 92 mg/kg (NCI 1978). In mice, there was a significant dose-related increase in the incidence of hepatocellular carcinomas in both males and females following 78 weeks of gavage administration at doses of 195 or 390 mg/kg/day (NCI 1978). These carcinomas were found in 10% of untreated control males, 12% of vehicle control males, 37% of low-dose males, and 76% of high-dose males. In female mice, they were found in 10% of untreated controls, 0% of vehicle controls, 33% of low-dose animals, and 89% of high-dose animals. In addition, there was a significant increase in the occurrence of adrenal pheochromocytomas (not specified as benign or malignant) in mice of both sexes at 390 mg/kg/day. These lesions, not found in the control or 195 mg/kg/day groups, had incidences of 17% in 390 mg/kg/day males and 28% in 390 mg/kg/day females. 1,1,2-Trichloroethane was classified as a possible human carcinogen in the Integrated Risk Information System (IRIS) (EPA 1987a) and as Group 3 (not classifiable as to its carcinogenicity in humans) by IARC (1999).

Data from a subcutaneous carcinogenicity study in Sprague-Dawley rats conducted by Norpoth et al. (1988) found that treatment with 1,1,2-trichloroethane for 2 years had no significant effect on the incidence of benign mesenchymal and epithelial tumors. Although there was a dose-related increased incidence of sarcomas in treated rats of both sexes compared to untreated controls, untreated controls showed an unusually low number of sarcomas, and this effect was not significant based on comparison to vehicle controls. A cancer initiation and promotion study in rats was also negative (Story et al. 1986).

2.20 GENOTOXICITY

1,1,2-Trichloroethane has been tested for genotoxicity in a variety of *in vivo* and *in vitro* test systems (see Tables 2-4 and 2-5). Mixed results have been obtained in *in vivo* tests. As shown in Table 2-4, 1,1,2-trichloroethane tested negative for sex-linked recessive lethal mutations in *Drosophila melanogaster* (Foureman et al. 1994). Although a weakly positive response was elicited in a mitotic recombination (eye mosaic) assay in *Drosophila*, this response was seen only at a cytotoxic concentration (Vogel and Nivard 1993). The frequency of micronucleated polychromatic erythrocytes in the bone marrow of male and female mice was not significantly affected by treatment with 1,1,2-trichloroethane (Crebelli et al. 1999). In a study that evaluated DNA damage (as measured by unwinding), 1,1,2-trichloroethane did not induce damage in mouse hepatocytes (Taningher et al. 1991). However, 1,1,2-trichloroethane tested positive for DNA adduct formation in rat and mouse liver, with adducts occurring to a greater extent in mice relative to rats (Mazzullo et al. 1986). The authors pointed out that there is a correlation between these adduct

formation results and species susceptibility to cancer, as the incidence of hepatocellular carcinomas was increased in mice, but not rats, given 1,1,2-trichloroethane for 78 weeks. Positive results were also seen in several assays that evaluated DNA synthesis in the hepatocytes of mice (Mirsalis et al. 1989; Miyagawa et al. 1995). The authors of these studies suggested that the induction of DNA synthesis may be an important mechanism of hepatocarcinogenicity (Mirsalis et al. 1989). Finally, 1,1,2-trichloroethane was positive for the inhibition of DNA synthesis in mice administered 1,1,2-triochloroethane via intratesticular injection (Borzelleca 1983).

Table 2-4. Genotoxicity of 1,1,2-Trichloroethane *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
Drosophila melanogaster (feed)	Sex-linked recessive lethal	–	Foureman et al. 1994
D. melanogaster (inhalation)	Mitotic recombination	+	Vogel and Nivard 1993
Mouse (intraperitoneal)	Micronuclei in bone marrow cells	–	Crebelli et al. 1999
Mouse (intraperitoneal)	DNA damage (unwinding) in hepatocytes	–	Taningher et al. 1991
Rat (intraperitoneal)	DNA adduct formation with liver DNA	+	Mazzullo et al. 1986
Mouse (intraperitoneal)	DNA adduct formation with liver DNA	+	Mazzullo et al. 1986
Mouse (gavage)	Unscheduled DNA synthesis in hepatocytes	–	Mirsalis et al. 1989
Mouse (gavage)	S-phase DNA synthesis in hepatocytes	+	Mirsalis et al. 1989
Mouse (gavage)	Replicative DNA synthesis in hepatocytes	+	Miyagawa et al. 1995
Mouse (intratesticular)	Inhibition of DNA synthesis in the testis	+	Borzelleca 1986

+ = positive results; – = negative results; DNA = deoxyribonucleic acid

Table 2-5. Genotoxicity of 1,1,2-Trichloroethane *In Vitro*

		Results		
		Activation		
Species (test system)	Endpoint	With	Without	Reference
Salmonella typhimurium (TA1535, TA98, TA100)	Gene mutation	–	–	Barber and Donish 1982
S. typhimurium (TA100, TA1535)	Gene mutation	–	–	Milman et al. 1988
S. typhimurium (TA1535, TA1537, TA98, TA100)	Gene mutation	–	–	Mitoma et al. 1985
S. typhimurium (TA1535)	Gene mutation	–	–	Rannug et al. 1978
S. typhimurium (BA13)	Gene mutation (Ara test)	–	–	Roldan-Arjona et al. 1991

Table 2-5. Genotoxicity of 1,1,2-Trichloroethane *In Vitro*

Species (test system)	Endpoint	Results: Activation: With	Results: Activation: Without	Reference
S. typhimurium (TA100)	Gene mutation	–	–	Simmon et al. 1977
S. typhimurium (TA97, TA98, TA100, TA1535, TA1537)	Gene mutation	–	–	Zeiger et al. 1988
Escherichia coli PQ37	Gene mutation	–	–	Mersch-Sundermann et al. 1989
E. coli WP2$_S$ (λ)	λ Prophage induction	+	+	DeMarini and Brooks 1992
Saccharomyces cerevisiae	Mitotic gene conversion	+	+	Bronzetti et al. 1987
Aspergillus nidulans P1	Chromosome malsegregation	NA	+	Crebelli et al. 1988
Human lymphocytes	Micronuclei	–	+	Tafazoli and Kirch-Volders 1996
Human AHH-1 cells	Micronuclei	NA	–	Doherty et al. 1996
Human MCL-5 cells	Micronuclei	NA	+	Doherty et al. 1996
Human lymphoblastoid cells	Micronuclei	NA	+	Doherty et al. 1996
Human lymphocytes	DNA damage	+	+	Tafazoli and Kirch-Volders 1996
Rat hepatocytes	DNA synthesis	NA	+	Reddy 1993
Rat hepatocytes	DNA repair	NA	+	Milman et al. 1988
Rat hepatocytes	DNA repair	NA	+	Williams 1983
Mouse hepatocytes	DNA repair	NA	–	Milman et al. 1988
Mouse hepatocytes	DNA repair	NA	–	Williams 1983
Calf thymus cells	DNA adduct formation	NA	+	DiRenzo et al. 1982a
Mouse BALB/c-3T3 cells	Cellular transformation	NA	+	Milman et al. 1988
Mouse BALB/c-3T3 cells	Cellular transformation	NA	–	Tu et al. 1985

– = negative result; + = positive result; DNA = deoxyribonucleic acid; NA = not applicable

Mixed results have also been obtained in *in vitro* assays of 1,1,2-trichloroethane (Table 2-5). In tests for reverse mutations in *Salmonella typhimurium*, results were consistently negative with and/or without metabolic activation in several strains (Barber and Donish 1982; Milman et al. 1988; Mitoma et al. 1985; Rannug et al. 1978; Roldan-Arjona et al. 1991; Simmon et al. 1977; Zeiger et al. 1988). 1,1,2-Trichloroethane tested weakly positive for prophage induction in *Escherichia coli* WP2 (DeMarini and Brooks 1992), but was not mutagenic to *E. coli* PQ37 strain in the SOS-chromotest (Mersch-Sundermann et al. 1989). Positive results were seen for mutagenicity and chromosome malsegregation in fungi (Bronzetti et

al. 1987; Crebelli et al. 1988). Human lymphocytes exposed to 1,1,2-trichloroethane showed an approximately 2-fold increase in micronuclei in the absence, but not the presence, of exogenous metabolic activation. It was noted that this response did not exhibit dose-dependent characteristics (Tafazoli and Kirsch-Volders 1996). In another study, increases in micronucleated cells observed in human lymphoblastoid and MCL-5 cell lines (approximately 3.5- and 4-fold, respectively, compared to controls) were statistically significant and dose-related. Kinetochore staining revealed dose-related increases in kinetochore-positive signals in both cell lines (Doherty et al. 1996). However, similar exposure of the AHH-1 cell line failed to induce micronuclei (Doherty et al. 1996). In the comet assay conducted by Tafazoli and Kirsch-Volders (1996), there was a 1,1,2-trichloroethane-induced DNA breakage in the presence and absence of exogenous metabolic activation. Tests of DNA repair were positive in rat hepatocytes, but negative in mouse hepatocytes (Milman et al. 1988; Williams 1983). Significant adduct formation of 1,1,2-trichloroethane with calf thymus DNA also occurred *in vitro* (DiRenzo et al. 1982a). In two cell transformation assays performed in the absence of activation on mouse BALB/c-3T3 cells, one result was negative and the other was positive (Milman et al. 1988; Tu et al. 1985). Although there are negative as well as positive results (reported in the absence of cytotoxicity), it is evident that this compound does have some genetic effects both *in vitro* and *in vivo*. The significance of these effects for humans is not clear, especially since results of *in vivo* mammalian assays showed species variability.

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

3.1 TOXICOKINETICS

Limited data on 1,1,2-trichloroethane in humans and animals are available. These data are summarized below.

- 1,1,2-Trichloroethane is rapidly absorbed through the respiratory tract in humans. In animals, 1,1,2-tricholoethane is rapidly absorb through the skin and is well-absorbed from the gastrointestinal tract.
- In animals and presumably humans, absorbed 1,1,2-trichloroethane is distributed throughout the body with the highest concentrations found in the fat, liver, and brain.
- The primary metabolites of 1,1,2-trichloroethane are chloroacetic acid (formed by cytochrome P-450), and S-carboxymethylcysteine and thiodiacetic acid (formed following conjugation with glutathione).
- The major route of excretion after oral exposure is via metabolites in the urine; smaller amounts of 1,1,2-trichloroethane are excreted in exhaled air and feces. Little 1,1,2-trichloroethane was detected in the urine following inhalation exposure in humans. The half-life of 1,1,2-trichloroethane in animals exposed via inhalation exposure was 49 minutes.

3.1.1 Absorption

Studies in humans indicate that 1,1,2-trichloroethane is absorbed rapidly after inhalation exposure (Morgan et al. 1970, 1972). In one of the studies (Morgan et al. 1970), a volunteer took one breath of radiolabeled 1,1,2-trichloroethane and expired 2–3% of the inspired dose in the alveolar air after 12 seconds and about 0.5% after 40 seconds of breath-holding. More than 90% of the administered dose was retained in the body after 50 minutes. These data indicate that 1,1,2-trichloroethane was extensively absorbed into the bloodstream, supported by a blood-air partition coefficient (K_D) of 44.2. Gargas et al. (1989) determined a blood:air partition coefficient in humans of 35.7.

Data on absorption of 1,1,2-trichloroethane following inhalation exposure in animals were generated in an effort to determine time courses for repeat exposure and to validate physiologically-based pharmacokinetic (PBPK) models. Rats and mice exposed to 1,1,2-trichloroethane under closed chamber conditions at 100 ppm 6 hours/day, 5 days/week for 4 weeks showed significant concentrations of 1,1,2-trichloroethane in the blood, indicating that 1,1,2-trichloroethane is extensively absorbed in both species (The Sapphire Group 2003). This is supported by the identification of a partition coefficient for

rats of 58.0 (Gargas et al. 1989). A supporting study (using few numbers of animals/time point and evaluating blood levels at a limited number of sampling intervals) found that the maximal blood concentrations after 4 weeks exposure were 2.2 µg/mL in rats and 2.1 µg/mL in mice (Poet 2003). The only other absorption information comes from the assumption that an administered chemical has been absorbed by the body if it can be shown to affect physiological processes. For example, following inhalation exposure to 1,1,2-trichloroethane under closed chamber conditions, exhalation of acetone was altered. This provides indirect evidence that 1,1,2-trichloroethane is absorbed following inhalation exposure.

In an effort to determine time courses for repeat exposure and to validate PBPK models, rats were administered 1,1,2-trichloroethane via gavage in corn oil at 92 mg/kg/day or in water at 1.7 mg/kg/day for 5 days. Similarly, mice were treated at 390 mg/kg/day in corn oil or 10 mg/kg/day in water. Significant concentrations of 1,1,2-trichloroethane were detected in the blood, indicating that 1,1,2-trichloroethane is well absorbed in both species. Maximal blood concentrations were observed in rats on day 1 (up to 17 µg/g) and in mice on days 3 and 5 (8.5 to 25 µg/g) (Poet 2003; The Sapphire Group 2003). The only other data available in animals showed that oral doses near the maximum tolerated dose in mice (300 mg/kg) or rats (70 mg/kg) were 81% metabolized, indicating that at least this amount was absorbed (Mitoma et al. 1985). This suggests that 1,1,2-trichloroethane, like other structurally related halocarbons, is well absorbed from the gastrointestinal tract of animals, and probably humans as well.

Two studies in animals indicate that 1,1,2-trichloroethane is easily absorbed through the skin. In the guinea pig, blood concentration of 1,1,2-trichloroethane peaked at ≈3.7 µg/mL within a half-hour following 1.0 mL 1,1,2-trichloroethane single epicutaneous application to the skin (Jakobson et al. 1977). Following the peak, the blood level declined to ≈2.5 µg/L at 1 hour, remained at this level until ≈4 hours, and then rose to ≈3.7 µg/L at 6 hours. The authors suggested that this complex dermal absorption of 1,1,2-trichloroethane in guinea pigs may be due to an initial increased barrier function of the skin after 1 hour, which led to decreased absorption. Subsequent absorption during the next few hours may represent an overcoming of the barrier. However, it is also possible that the prolonged time-course for dermal absorption could reflect retention of 1,1,2-trichloroethane in skin lipids. In mice, 15 minutes after application of 0.5 mL of 1,1,2-trichloroethane, 99.7% was retained in the body and 0.3% was expired in the breath (Tsuruta 1975). The absorption rate was calculated to be 130 nmoles/minute/cm^2 of skin. The rapid absorption through the skin may well be due to the highly lipid soluble character of 1,1,2-trichloroethane (Kronevi et al. 1977).

3.1.2 Distribution

After an inhalation exposure of 1,000 ppm for 1 hour in mice, 1,1,2-trichloroethane was distributed in the following manner: approximately 600 µg/g in fats, 80 µg/g in the kidney and liver, 45–60 µg/g in the blood and brain, and 20–35 µg/g in the heart, spleen, and lung (Takahara 1986a). Examination of partition coefficients showed that 1,1,2-trichloroethane had a moderate degree of lipid solubility compared to other hydrocarbons, but was still quite lipid soluble (Gargas et al. 1989; Morgan et al. 1972; Sato and Nakajima 1979). Poet (2003) measured partition coefficients in rat brain and spleen and in mouse blood. Partition coefficients for 1,1,2-trichloroethane were 43 for rat spleen:air, 56 for rat brain:air, and 71 for mouse blood:air. Rat liver:air and fat:air partition coefficients of 73.1 and 1,438, respectively, were determined by Gargas et al. (1989). This indicates that 1,1,2-trichloroethane could be easily distributed and retained in fat, liver, and brain in both animals and humans.

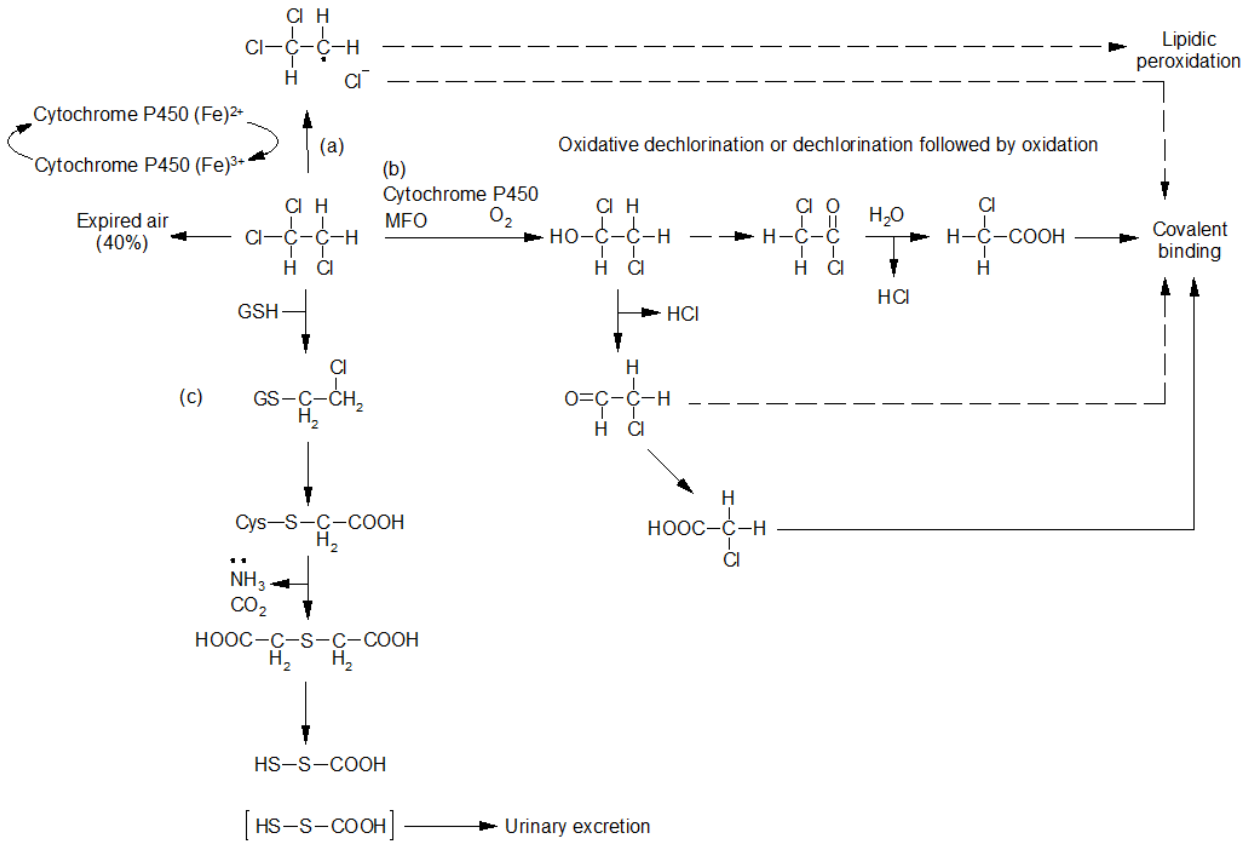
Limited information is available on the distribution of 1,1,2-trichloroethane following oral exposure. One study showed that 1,1,2-trichloroethane was distributed to the liver following oral exposure in animals (Mitoma et al. 1985). In this study, 1,1,2-trichloroethane was extensively metabolized (presumably by the liver), and was also found to bind to hepatic protein. It is likely that 1,1,2-trichloroethane is also distributed to the liver in humans.

3.1.3 Metabolism

The primary metabolites identified by high-performance liquid chromatography in rats and mice given 1,1,2-trichloroethane by gavage were chloroacetic acid, S-carboxymethylcysteine, and thiodiacetic acid (Mitoma et al. 1985). An earlier study reported these three compounds to be the primary metabolites of 1,1,2-trichloroethane following intraperitoneal injection in mice (Yllner 1971). S-Carboxymethylcysteine and thiodiacetic acid are formed from 1,1,2-trichloroethane following conjugation with glutathione (Yllner 1971). Chloroacetic acid is formed by hepatic cytochrome P-450 (Ivanetich and Van Den Honert 1981). This reaction is thought to proceed via oxidative dechlorination of 1,1,2-trichloroethane. Cytochrome P-450 can also apparently produce free radicals from 1,1,2-trichloroethane (Mazzullo et al. 1986). These proposed pathways are shown in Figure 3-1. Acyl chlorides and free radicals are reactive metabolites that can bind to proteins and nucleic acids, and are suspected of being cytotoxic, mutagenic, and carcinogenic (Ivanetich and Van Den Honert 1981; Mazzullo et al. 1986). Acyl chlorides conjugated with GSH generate S-carboxymethylcysteine and thiodiacetic acid, which are major urinary metabolites of 1,1,2-trichloroethane (Yllner 1971). Other metabolites, found only in trace amounts in mice and rats following exposure to 1,1,2-trichloroethane, included trichloroacetic acid and trichloroethanol (Ikeda and

Ohtsuji 1972; Takahara 1986b; Yllner 1971). It is not clear how these compounds were formed; it was suggested by Yllner (1971) that they might be derived from impurities in the 1,1,2-trichloroethane samples used.

Figure 3-1. Proposed Metabolic Pathway of 1,1,2-Trichloroethane*



- - - supposed pathway
----- proven pathway

*(a) one-electron oxidation; (b) two-electron oxidation; (c) detoxification step

Source: Mazzullo et al. 1986 (based on studies in rats and mice)

Although percent of the orally-administered dose metabolized was identical in rats and mice (81%), the actual amount of 1,1,2-trichloroethane metabolized was much higher in mice (Mitoma et al. 1985). The chemical was given to each species at the maximum tolerated dose, which was 4.3 times greater in mice; mice experienced a higher body burden than rats, but were able to metabolize the same percentage of it. The inherent ability of mice to metabolize 1,1,2-trichloroethane at a higher rate than rats may contribute to the greater susceptibility of mice to 1,1,2-trichloroethane cytotoxicity and carcinogenicity (Ivanetich

and Van Den Honert 1981; Mazzullo et al. 1986). It is not known how the rate of 1,1,2-trichloroethane metabolism in humans compares to that in mice and rats. However, metabolism in humans is likely to be qualitatively similar to that in animals.

3.1.4 Excretion

The excretion rate of inhaled 1,1,2-trichloroethane in humans was measured in the breath and urine of humans (Morgan et al. 1970). Excretion in the breath after 1 hour was 2.9% of the administered dose; the slope of the retention curve was 0.006. The excretion rate in the urine was <0.01%/minute of administered radioactivity. From these data, the half- life for urinary excretion was estimated to be about 70 minutes.

Poet (2003) performed breath analysis in female mice exposed to 1,1,2-trichloroethane at 250 and 500 ppm for 4–6 hours. The half-life following 1-hour inhalation exposure to 1,005 ppm of 1,1,2-trichloroethane in mice was determined to be 625 minutes in the heart, 203 minutes in the fat, 147 minutes in the brain, 127 minutes in the spleen, 122 minutes in the lungs, 43 minutes in the kidney, 39 minutes in the blood, and 19 minutes in the liver (Takahara 1986a). The half-life in the whole body was calculated to be 49.3 minutes. The presence of 1,1,2-trichloroethane in tissue samples was determined by gas chromatography.

The excretion routes were shown to be similar in rats and mice, regardless of whether the chemical was given orally (Mitoma et al. 1985) or intraperitoneally (Yllner et al. 1971). Following a dose of radiolabeled compound, about 7–10% of 1,1,2-trichloroethane was exhaled unchanged in the breath, 3–7% was exhaled as CO_2, 72–87% was found as metabolites in the urine, about 1% was in the feces, and 1–3% remained in the carcasses of rats and mice after 48 hours. It is not known how excretion of 1,1,2-trichloroethane in humans compares to that in mice and rats, but (in the absence of additional information), it is likely that excretion in humans is primarily via metabolites in the urine.

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

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

species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic endpoints.

PBPK models were developed to extrapolate from the oral route of exposure to the inhalation route of exposure. The Sapphire Group (2003) determined K_m and V_{max} and, utilizing data from pharmacokinetic experiments by Poet (2001), developed and validated a PBPK model to predict the disposition of 1,1,2-trichloroethane in mice and rats for inhalation and ingestion. The optimized model included suicide inhibition (i.e., enzyme destruction via inactivation by bound, reactive intermediate) as a mechanism by which a reduction in V_{max} was seen in female mice after exposure. The initial PBPK model (The Sapphire Group 2003) was expanded and refined to model the following endpoints: immunotoxicity in mice (The Sapphire Group 2004a), acute neurotoxicity in rats (The Sapphire Group 2004b), subchronic neurotoxicity in rats (The Sapphire Group 2005a), reproduction in rats (The Sapphire Group 2006), development in rats (The Sapphire Group 2005b), and carcinogenicity in rats and mice (The Sapphire Group 2004c). These PBPK models are designed to predict inhalation exposure levels equivalent to those used in oral toxicity studies in rodents (based on selection of a critical endpoint and using the most appropriate internal dose measure) and are not applicable to humans.

3.1.6 Animal-to-Human Extrapolations

There are no data available that evaluate the sensitivity of humans to 1,1,2-trichloroethane-induced toxicity relative to animals. Lethality data in animals do not suggest a high degree of interspecies variability; however, available information suggests that species differences in metabolism (among rats and mice) may affect susceptibility. In both species, lethality was observed following inhalation exposures >400 ppm and following oral exposures >300 mg/kg, with effects being seen at slightly lower levels of exposure in mice than rats. Based on data from one study, the absorption of 1,1,2-trichloroethane is expected to be similar in rats and mice; similar concentrations of 1,1,2-trichloroethane were detected in the blood of rats and mice after 4 weeks of inhalation exposure to 1,1,2-trichloroethane (Poet 2003). In another study, the primary metabolites in rats and mice administered 1,1,2-trichloroethane by gavage were identified as chloroacetic acid, S-carboxymethylcysteine, and thiodiacetic acid (Mitoma et al. 1985). The metabolites of 1,1,2-trichloroethane, rather than the parent compound, is thought to be responsible for most of its health effects, owing to greater reactivity of the metabolites. Data from the study by Mitoma et al. (1985) also suggest that mice may have an inherent ability to metabolize 1,1,2-trichloroethane at a higher rate than rats; this may contribute to the greater susceptibility of mice to the

toxicity of 1,1,2-trichloroethane than rats. In support, Mazzullo et al. (1986) showed increased binding of 1,1,2-trichloroethane to DNA from murine organs (liver, lung, stomach, and kidney) relative to rat organs. Although the metabolism of 1,1,2-trichloroethane is expected to be similar to that seen in animals, it is not known how the rate of metabolism in humans compares to that in mice and rats. Data from studies of other compounds, such as trichloroethylene (TCE) or perchloroethylene (PCE), suggest that humans absorb and metabolize less of these halocarbons than rats (Bernauer et al. 1996; Green et al. 1997; NAS 2009; Volkel et al. 1998); however, specific data comparing the metabolism of 1,1,2-trichloroethane in humans and rats were not identified. Owing to the increased surface area of the olfactory epithelium of rats relative to humans, rats may be a particularly sensitive model for chemically-induced injury to these tissues.

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 1,1,2-trichloroethane are discussed in Section 5.7, Populations with Potentially High Exposures.

The results from two intermediate-duration oral studies in rats suggest that immature rats were not more susceptible to the toxic effects of 1,1,2-trichloroethane than mature rats. In a two-generation study, decreased body weight gain during gestation was observed in P1 and F1 females administered 1,1,2-trichloroethane in drinking water at 82 mg/kg/day; effects in pups (decreased weights on postnatal days 4 to 21) were observed at the same dose (Mylchreest 2006). In a developmental study, female rats treated at 111 mg/kg/day in drinking water on days 6–20 of gestation showed decreased body weight

gain; this effect occurred in the absence of significant, treatment-related effects on fetal weight, sex, or the incidences of external, visceral, or skeletal abnormalities (Wilson 2005). However, few data are available to assess the susceptibility of children to 1,1,2-trichloroethane .

Persons with diabetes (Hanasono et al. 1975), with prior exposure to polybrominated biphenyls (PBBs) (Kluwe et al. 1978), or with prior exposure to isopropyl or ethyl alcohol or acetone (Traiger and Plaa 1974) may be more susceptible to the hepatotoxic effects of 1,1,2-trichloroethane. It is possible that prior exposure to drugs or chemicals that induce enzyme activity (including cytochrome P-450) could have the same effect.

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 (IOM 2010; NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (IOM 2010; NAS/NRC 1989). 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 1,1,2-trichloroethane are discussed in Section 3.3.1. 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 1,1,2-trichloroethane from this report are discussed in Section 5.6, General Population Exposure.

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 (IOM 2010; NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effect caused by 1,1,2-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

Currently, biomarkers for 1,1,2-trichloroethane do not adequately capture exposure, possibly due to 1,1,2-trichloroethane's short half-life. No epidemiology studies were conducted that assessed exposure by measuring 1,1,2-trichloroethane levels in the blood or urine and associated health effects. 1,1,2-Trichloroethane and its metabolites have been detected in blood, urine, expired air, and tissues of humans and animals (Jakobson et al. 1977; Mitoma et al. 1985; Morgan et al. 1970; Poet 2003; Takahara 1986a; The Sapphire Group 2003; Tsuruta 1975). The parent compound was measured in the blood and expired air; its primary metabolites (chloroacetic acid, S-carboxymethylcysteine, and thiodiacetic acid) have been detected in the urine (Mitoma et al. 1985). Based on data from 2003–2004, 2005–2006, 2007–2008, 2009–2010, and 2011–2012 NHANES, levels of blood 1,1,2-trichloroethane were less than the limit of detection (CDC 2017). Levels below the limit of detection or only trace amounts of 1,1,2-trichloroethane have been reported in exhaled air (Wallace et al. 1984). Low levels of 1,1,2-trichloroethane were likewise detected in the tissues of humans soon after they were exposed primarily via inhalation (Bauer 1981a, 1981b), exemplifying that it is difficult to assess lower levels of exposure to 1,1,2-trichloroethane with current methodologies.

3.3.2 Biomarkers of Effect

No studies were located that identified biomarkers specific for 1,1,2-trichloroethane-induced disease states. None of the available epidemiological studies (Brender et al. 2014; Dosemeci et al. 1999) identified alterations in blood chemistry indices or other pathological endpoints that could be used to identify the disease state. Biomarkers for diagnosis of target organ toxicity (e.g., AST for liver damage) may be considered a biomarker of effect if it is known that exposure to 1,1,2-trichloroethane occurred.

3.4 INTERACTIONS WITH OTHER CHEMICALS

PBBs were shown to increase the renal toxicity of 1,1,2-trichloroethane as measured by decreases in p-aminohippurate accumulation in renal cortical slices (Kluwe et al. 1978). PBBs are known to increase the activities of microsomal mixed-function oxygenases in the kidney and liver, so increased metabolism of 1,1,2-trichloroethane and the increased presence of metabolites more toxic than the parent compound itself are likely responsible for the increased toxicity of 1,1,2-trichloroethane in the kidney. However, the study also showed that PBBs did not increase the hepatotoxic effects of 1,1,2-trichloroethane in mice, as indicated by relative liver weight or AST levels.

Phenobarbital, another microsomal enzyme inducing agent, was found to potentiate liver toxicity, as indicated by increases in AST and ALT in rats that were exposed to 1,1,2-trichloroethane vapor (Carlson 1973). Guinea pigs treated with pentobarbital as an anesthetic following dermal application of 1,1,2-trichloroethane were shown to produce reduced glycogen levels and hydropic changes in the liver (Kronevi et al. 1977). Liver effects were not found in anesthetized "control" animals or animals that were treated with 1,1,2-trichloroethane, but not anesthetized. The authors suggest that the liver effects they observed were produced by the interaction of pentobarbital and 1,1,2-trichloroethane. The lack of untreated controls makes this claim difficult to evaluate, however. Potentiation is usually seen only after pretreatment with the inducer, since time is required for enzyme induction. It may be that dermal absorption of 1,1,2-trichloroethane was slow enough, compared to intraperitoneal absorption of pentobarbital, for this to occur.

Pretreatment with lower, but not higher, doses of acetone (MacDonald et al. 1982) potentiated the hepatotoxicity of 1,1,2-trichloroethane in rats as indicated by a rise in ALT and a decrease in hepatic GSH levels. Acetone also potentiated the 1,1,2-trichloroethane-induced elevation of ALT in mice (Traiger and Plaa 1974).

Pretreatment with isopropyl alcohol (Traiger and Plaa 1974) or ethanol (Klaassen and Plaa 1966) potentiated the 1,1,2-trichloroethane-induced elevation of ALT activity in mice. Pretreatment with ethanol did not alter bromosulfophthalein retention (Klaassen and Plaa 1966).

Pretreatment with alloxan, which induces a hyperglycemic state similar to that found in diabetic humans, also enhanced the hepatotoxic effects of 1,1,2-trichloroethane in rats as indicated by increased ALT

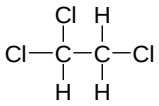
activity and increased hepatic triglyceride concentration (Hanasono et al. 1975). The mechanism of this interaction is unknown.

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Data pertaining to the chemical identity of 1,1,2-trichloroethane are listed in Table 4-1.

Table 4-1. Chemical Identity of 1,1,2-Trichloroethane

Characteristic	Information	Reference
Chemical name	1,1,2-trichloroethane	CAS 1988
Synonym(s) and registered trade name(s)	Ethane trichloride; β-Trichloroethane; Vinyl trichloride; 1,2,2-Trichloroethane	CAS 1988; SANSS 1988
Chemical formula	β-T; Cement T-339	SANSS 1988
Chemical structure		CAS 1988
Identification numbers:		
CAS Registry	79-00-5	CAS 1988

CAS = Chemical Abstracts Services

4.2 PHYSICAL AND CHEMICAL PROPERTIES

The physical and chemical properties of 1,1,2-trichloroethane are presented in Table 4-2.

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

Property	Information	Reference
Molecular weight	133.41 g/mol	Riddick et al. 1986
Color	Colorless	Hawley 1981
Physical state	Liquid	Hawley 1981
Melting point	-36.53°C	Riddick et al. 1986
Boiling point	113.85°C	Riddick et al. 1986
Density at 20°C	1.43931 1.4416 1.443	Riddick et al. 1986 Merck 1983 Torkelson and Rowe 1981
Odor	Sweet	Hawley 1981
Solubility:		
Water at 20°C	4,400 mg/L	Riddick et al. 1986
Organic solvents	Miscible with ethers, alcohols, esters, and ketones	Hawley 1981

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

Property	Information	Reference
Partition coefficients:		
Log K_{ow}	2.42	Isnard and Lambert 1988
Log K_{oc}	1.06–2.49[a] (estimated)	Sabljic 1987
Vapor pressure at 25°C	22.49 mmHg	Riddick et al. 1986
Henry's law constant	$9.1x10^{-4}$ atm/m^3-mol (25°C) $1.12x10^{-3}$ atm/m^3-mol (30°C)[b]	Ashworth et al. 1988
Autoignition temperature	460°C	Parrish 1983
Flashpoint	None	Hawley 1981
Flammability limits	8.4–13.3% (by volume)	Moolenaar and Olson 1989
Conversion factors:		
ppm (v/v) to mg/m^3 in air (20°C)	1 ppm (v/v) = 5.55 = mg/m^3	
mg/m^3 (v/v) to ppm in air (20°C)	1 mg/m^3 = 0.18 ppm (v/v)	

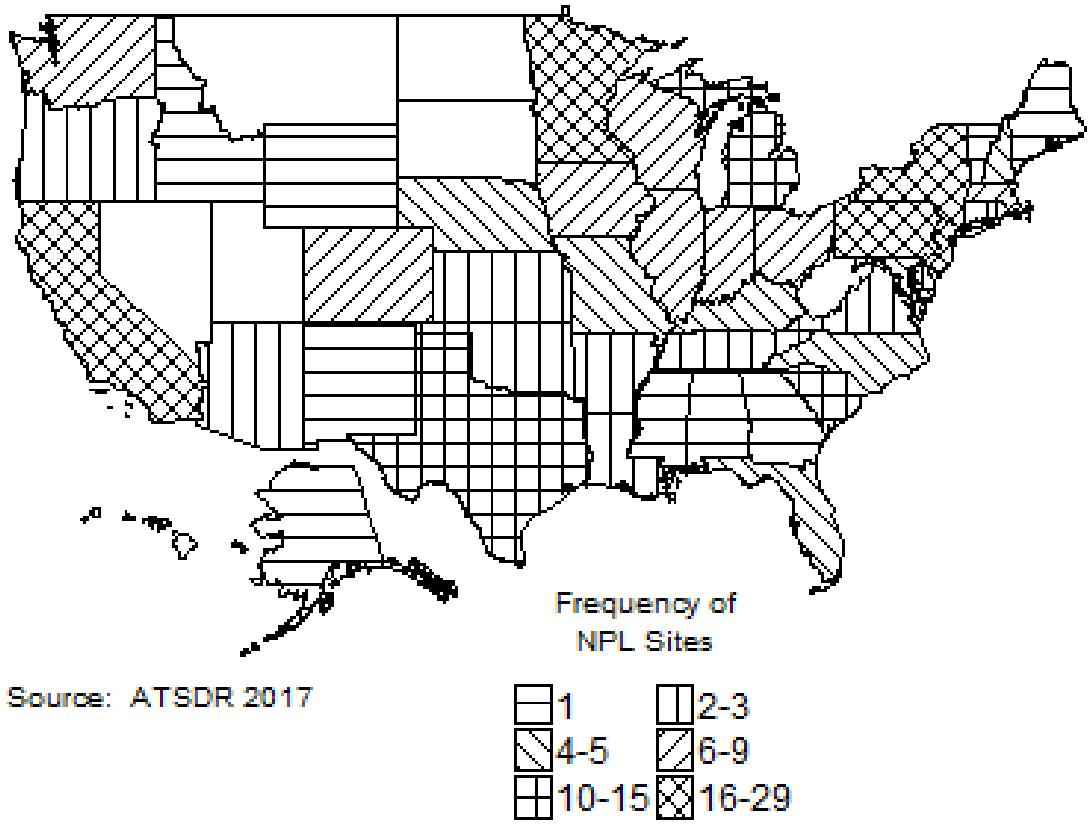
[a]Organic matter partition coefficient.
[b]First value obtained using equilibrium partitioning in closed systems technique and second by the batch air-stripping method.

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

1,1,2-Trichloroethane has been identified in at least 263 of the 1,854 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2017). However, the number of sites in which 1,1,2-trichloroethane has been evaluated is not known. The number of sites where 1,1,2-trichloroethane is found (in the air, water, or soil) in each state is shown in Figure 5-1. Of these sites, 262 are located within the United States and 1 is located in the Virgin Islands (not shown).

Figure 5-1. Number of NPL Sites with 1,1,2-Trichloroethane Contamination



- The general population may be exposed to low levels of 1,1,2-trichloroethane through inhalation of contaminated air and ingestion of contaminated well water (exposure via drinking water is uncommon based on monitoring data for groundwater supplies).

- People who live or work near industries that produce or use 1,1,2-trichloroethane could most likely be exposed from contaminated air (from emissions and volatilization from waste water).

- 1,1,2-Trichloroethane does not absorb appreciably to suspended solids, sediment, or soil.
- 1,1,2-Trichloroethane undergoes anaerobic biodegradation in groundwater and sediment and volatilization in surface water. 1,1,2-Trichloroethane in the air is oxidized by hydroxyl radicals.

1,1,2-Trichloroethane is predominantly a man-made chemical whose presence in the environment results from anthropogenic activity. This chemical has also been identified as an intermediate in the biodegradation of 1,1,2,2-tetrachloroethane, another man-made chemical. It is made commercially by the chlorination of ethylene with chlorine or by the oxychlorination of ethylene with HCl and oxygen. It is primarily used as a captive intermediate in the manufacture of 1,1-dichloroethene (vinylidene chloride), but may also be used as a solvent, especially in chlorinated rubber manufacture. Production and use information are proprietary; however, effluent monitoring data indicate that high levels (>100 ppb) of discharge are associated with laundries, and the organic chemicals and mechanical products industries (Table 5-1). The maximum levels in these waste waters were 109–250 ppb. Gaseous releases include vent gas and fugitive emissions from the production and use of 1,1,2-trichloroethane as well as volatilization from waste water and municipal treatment plants. Releases to soil are expected to involve the landfilling of sludge and process residues. Based on the release pattern of other chlorinated ethanes and ethenes, it is expected that the release pattern for 1,1,2-trichloroethane is 70–90% to air, 10–30% to land, and a few percent to water. No use with significant consumer or general population exposures has been identified.

Table 5-1. Sources of 1,1,2-Trichloroethane Effluents[a]

		Concentration (ppb)		
Industry	Frequency	Maximum	Medium	Low
Timber products	1	18.46	18.46	18.46
Organics and plastics	1	7.12	7.12	7.12
Inorganic chemicals	2	6.00	4.00	2.01
Plastics and synthetics	2	31.85	3.65	0.26
Auto and other laundries	1	108.99	108.99	108.99
Organic chemicals	1	203.77	203.77	203.77
Mechanical products	4	249.52	45.74	1.33
Transportation equipment	3	75.33	66.34	24.53
Synfuels	1	2.43	2.43	2.43
Publicly owned treatment works	4	15.22	1.20	0.42

[a]Discharges to water.

Source: Shackelford et al. 1983

If 1,1,2-trichloroethane is released into soil, it is expected to partially leach into the subsurface and groundwater (because it has a low soil adsorption coefficient), and to partially volatilize. In groundwater, it will be subject to anaerobic biodegradation; however, no information concerning reaction rates is available. Biodegradation is expected to occur in sediment and landfills when anaerobic conditions are present. The mechanism for biodegradation is reductive dehalogenation, which leads to the formation of vinyl chloride, a human carcinogen (USDHHS 1985). From the limited data available, biodegradation under aerobic conditions, such as exists in surface soil, will be very slow, at best. In surface water, volatilization is the primary fate process (half-life 4.5 hours in a model river). Adsorption to sediment, bioconcentration in aquatic organisms, aerobic biodegradation, and hydrolysis are thought to be negligible by comparison. In the atmosphere, the dominant removal process is expected to be oxidation by photochemically-generated hydroxyl radicals, which proceeds by H-atom abstraction (estimated half-life 49 days). The radical so produced subsequently reacts with atmospheric oxygen and other atmospheric gases (methane, carbon monoxide, and others). Removal from the atmosphere is also thought to occur from washout by precipitation; however, most of the 1,1,2-trichloroethane removed by this process is expected to reenter the atmosphere by volatilization. Because oxidation in the atmosphere is slow, considerable dispersion of 1,1,2-trichloroethane from source areas would be expected to occur. Thus, it is conceivable that 1,1,2-trichloroethane could be transported from other countries where it may be more widely used.

The general population may be exposed to low levels of 1,1,2-trichloroethane through inhalation of contaminated ambient air. Limited environmental monitoring data suggest that roughly one-quarter to one-half of the urban population may be so exposed. Where 1,1,2-trichloroethane is found, levels appear to be about 10–50 ppt. Results from a nationwide monitoring study of groundwater supplies show that exposure to 1,1,2-trichloroethane from contaminated drinking water appears to be uncommon (Westrick et al. 1984). However, in a New Jersey survey, 6.7% of the wells contained detectable levels of 1,1,2-trichloroethane; the most polluted wells being associated with urban land use (Greenberg et al. 1982; Page 1981). It is difficult to assess occupational exposure because data on current production and use are unavailable. A National Occupational Exposure Survey (NOES) by the National Institute of Occupational Safety and Health (NIOSH) through May 1988 estimated that 1,036 employees were potentially exposed to 1,1,2-trichloroethane in the United States. Occupational exposure will be primarily via inhalation.

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

In 1988, 1,1,2-Trichloroethane was produced by Dow Chemical U.S.A. in Freeport, Texas and by Olin Corporation in Seward, Illinois (SRI 1988). No production figures are available. It is produced in the United States from ethylene. In one method of preparation, ethylene is chlorinated to give 1,2-dichloroethane, which is then reacted with chlorine to give 1,1,2-trichloroethane (Archer 1979). A second method is via the oxychlorination of ethylene with hydrogen chloride and oxygen at 280–37°C in the presence of a catalyst (Archer 1979). 1,2-Dichloroethane and higher chlorinated ethanes are also formed in this process. 1,1,2-Trichloroethane is also produced as a coproduct in the thermal chlorination of 1,1-dichloroethane to produce 1,1,1-trichloroethane, especially when the reaction is carried out in the liquid phase (Archer 1979).

The only information pertaining to the amount of 1,1,2-trichloroethane produced dates back to 1979, when it was estimated that approximately 412 million pounds were produced (Thomas et al. 1982). This figure is the quantity of 1,1,2-trichloroethane required for maximum potential production of 1,1-dichloroethene (vinylidene chloride) and may be an overestimate because 1,1-dichloroethene can also be produced from 1,1,1-trichloroethane (Thomas et al. 1982). The exact quantity manufactured is proprietary information of Dow Chemical Corporation, which was the sole producer of 1,1,2-trichloroethane at that time. Most of the chemical was captively consumed as a precursor for 1,1-dichloroethene; however, according to a spokesperson from Dow, a quantity said to be in the 'low millions of pounds' is used annually in other industries (Thomas et al. 1982). It is not known whether the consumption of 1,1,2-trichloroethane has changed appreciably since 1979.

1,1,2-Trichloroethane is sometimes present as an impurity in commercial samples of 1,1,1-trichloroethane and trichloroethylene (Henschler et al. 1980; Tsuruta et al. 1983). 1,1,2-Trichloroethane has been shown to be formed during the anaerobic biodegradation of 1,1,2,2-tetrachloroethane; anaerobic conditions may occur in groundwater or in landfills (Bouwer and McCarty 1983; Hallen et al. 1986).

Table 5-2 summarizes information on U.S. companies that manufactured or used 1,1,2-trichloroethane in 2016 (TRI16 2017).

Table 5-2. Facilities that Produce, Process, or Use 1,1,2-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	9, 12
IL	1	1,000	9,999	12
KS	1	10,000	99,999	1, 5
KY	1	1,000,000	9,999,999	1, 3, 6
LA	10	0	9,999,999	1, 3, 5, 6, 12, 13, 14
MN	1	10,000	99,999	11
NY	1	10,000	99,999	6
OH	2	1,000	99,999	12
OR	1	10,000	99,999	12
TX	8	10,000	9,999,999	1, 3, 4, 5, 6, 12, 13, 14

[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: TRI16 2017 (Data are from 2016)

5.2.2 Import/Export

Data pertaining to the import/export of 1,1,2-trichloroethane were not located in the available literature.

5.2.3 Use

The principal use of 1,1,2-trichloroethane is as a chemical intermediate in the production of 1,1-dichloroethene (Archer 1979). There is no information available on the uses of the 'low millions of pounds' that were said to have been sold to other industries by Dow Chemical. 1,1,2-Trichloroethane finds limited use as a solvent where its high solvency is needed, such as for chlorinated rubbers (Archer 1979). It may be used as a solvent for fats, oils, waxes, and resins (Hawley 1981). Some 1,1,2-trichloroethane was sold for use in consumer products (Thomas et al. 1982). There was no indication in the literature as to what these products were. Moolenaar and Olson (1989), in a written communication as spokesmen for the Dow Chemical Company, a major producer of 1,1,2-trichloroethane, however, stated

that they are not aware of any consumer uses and that the Dow Chemical Company screens potential customers to determine how they intend to use it.

5.2.4 Disposal

1,1,2-Trichloroethane has been disposed of by adsorption on a suitable sorbent such as vermiculite, dry sand, or earth and placement in a secure landfill (NLM 1988). This method is not recommended, however (NLM 1988), although no alternative method was discussed in the available literature. The method of disposal recommended for most chlorinated solvents is incineration.

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 2005). 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 is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005).

5.3.1 Air

Estimated releases of 43,506 pounds (~19.73 metric tons) of 1,1,2-trichloroethane to the atmosphere from 27 domestic manufacturing and processing facilities in 2016, accounted for about 74% of the estimated total environmental releases from facilities required to report to the TRI (TRI16 2017). These releases are summarized in Table 5-3.

Table 5-3. Releases to the Environment from Facilities that Produce, Process, or Use 1,1,2-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	2	0	0	0	0	2	0	2
IL	1	1	0	0	3	0	1	3	4
KS	1	0	0	0	0	50	0	50	50
KY	1	983	35	0	0	0	1,018	0	1,018
LA	10	20,862	46	0	6	0	20,908	6	20,914
MN	1	17,636	0	0	0	0	17,636	0	17,636
NY	1	1,150	0	0	0	0	1,150	0	1,150
OH	2	4	0	0	0	0	4	0	4
OR	1	0	0	0	14,883	0	14,883	0	14,883
TX	8	2,868	0	0	5	0	2,873	0	2,873
Total	27	43,506	81	0	14,897	50	58,475	59	58,534

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

RF = reporting facilities; UI = underground injection

Source: TRI16 2017 (Data are from 2016)

1,1,2-Trichloroethane is emitted in vent gas when produced by the oxychlorination of ethylene dichloride (Liepins et al. 1977). Environmental releases of 1,1,2-trichloroethane from 1,1-dichloroethene manufacture are small; an EPA study found no 1,1,2-trichloroethane in process vent gas (Thomas et al. 1982). 1,1,2-Trichloroethane is formed in small quantities and may be released in vent gas or fugitive emissions during the production of other chlorinated hydrocarbons, for example, 1,2-dichloroethane and 1,1,1-trichloroethane (Thomas et al. 1982). Fugitive emission from its use as a solvent and volatilization from waste water constitute the major environmental release of 1,1,2-trichloroethane. An estimate of the

total release of 1,1,2-trichloroethane was made for 1979 by comparing ambient levels of 1,1,1-trichloroethane and 1,1,2-trichloroethane in urban air and releases of 1,1,1-trichloroethane (Thomas et al. 1982). The annual amount of 1,1,2-trichloroethane released annually was calculated to be 10,000–20,000 million tons.

A correlation of data from the EPA Air Toxics Emission Inventory with industrial source categories (SIC codes) shows that volatile emissions of 1,1,2-trichloroethane are associated with plastic materials and resins, industrial organic chemicals, petroleum refining, gaskets-packing and sealing devices, plating and polishing, residential lighting fixtures, radio and TV communication equipment, electronic components, motor vehicles parts and accessories, engineering and scientific instruments, photographic equipment, and supplies (SIC Codes 2821, 2869, 2911, 3293, 3471, 3645, 3662, 3679, 3714, 3811, 3861) (EPA 1987a).

Volatile organic compound (VOC) emissions are observed at solid waste landfills (these emissions are 2.6 times greater in a wet climate than a dry one [Vogt et al. 1987]). Therefore low levels of 1,1,2-trichloroethane may be expected in landfill gases from NPL sites.

5.3.2 Water

Estimated releases of 81 pounds (~0.04 metric tons) of 1,1,2-trichloroethane to surface water from 27 domestic manufacturing and processing facilities in 2016, accounted for about 0.14% of the estimated total environmental releases from facilities required to report to the TRI (TRI16 2017). These releases are summarized in Table 5-3.

Waste water streams from the production of 1,1,2-trichloroethane by liquid-phase chlorination of ethylene dichloride and the oxychlorination of ethylene dichloride with HCl contain 1,1,2-trichloroethane (Liepins et al. 1977). Information on industries that discharge 1,1,2-trichloroethane, the frequency of discharge, and concentration levels can best be obtained from the results of a comprehensive waste water survey conducted by the Effluent Guidelines Division of the EPA shown in Table 5-1. Over 4,000 samples of waste water from a broad range of industrial facilities and publicly-owned treatment works were analyzed in this survey. While the percentage of industries in a particular category containing 1,1,2-trichloroethane or the volume of waste water generated by them was not indicated, the data suggest that significant amounts of 1,1,2-trichloroethane are released into waterways nationwide (see Table 5-1). Between 1980 and 1988, 707 samples of waste water in EPA's STORET database were analyzed for 1,1,2-trichloro-

ethane (STORET 1988). Ten percent of the samples contained ≥10 ppb concentrations of 1,1,2-trichloroethane and the maximum level obtained was 360 ppb. Unfortunately, the detection limit is apparently recorded when no chemical is detected, so it is impossible to say whether the 90 percentile figure represents the sample above or below the limit of detection. EPA investigated priority pollutants in 40 geographically distributed publicly-owned treatment works (POTWs) representing a variety of municipal treatment technologies, size ranges, and industrial flow conditions. In this study, 1,1,2-trichloroethane was detected in 7% of influent samples, 3% of effluent samples, and 4% of raw sludge samples at maximum concentrations of 135, 6, and 2,100 ppb, respectively (EPA 1982c).

1,1,2-Trichloroethane was found at concentrations of 2.1, 26, and 180 ppb in three outfalls from the Dow Chemical of Canada plant into the St. Clair River for a net loading of 3.5 kg/day (King and Sherbin 1986). Puddles containing chlorinated hydrocarbons had been discovered on the bottom of the St. Clair River, which received these effluents (Kaiser and Comba 1986; King and Sherbin 1986). These chemicals are thought to be products or byproducts of chlorinated hydrocarbons manufactured at this site. Waste from this operation is now being incinerated but was historically landfilled. Landfill leachate from the landfill is treated with carbon and then discharged into a ditch leading to the St. Clair River. The concentration of 1,1,2-trichloroethane before and after treatment was 1,300 and 1,800 ppb. However, the carbon filter was reportedly spent (owing to saturation of the carbon) at the time of the survey.

1,1,2-Trichloroethane was detected in two samples at 2–3 ppb from Eugene, Oregon in the National Urban Runoff Program, in which 86 samples of runoff from 19 cities throughout the United States were analyzed (Cole et al. 1984). Runoff water from NPL hazardous waste sites containing 1,1,2-trichloroethane might be contaminated with this pollutant. No monitoring studies of runoff water from wastes sites were found in the available literature.

5.3.3 Soil

Estimated releases of 14,897 pounds (~6.76 metric tons) of 1,1,2-trichloroethane to soil from 27 domestic manufacturing and processing facilities in 2016, accounted for about 25.45% of the estimated total environmental releases from facilities required to report to the TRI (TRI16 2017). These releases are summarized in Table 5-3.

No information on the release of 1,1,2-trichloroethane to soil was found in the available literature. It is anticipated that process residues and sludge containing this chemical may be landfilled (Jackson et al.

1984). In an experiment designed to simulate the anaerobic conditions for biodegradation in landfills, 1,1,2-trichloroethane was found to be a biodegradation product of 1,1,2,2-tetrachloroethane (Hallen et al. 1986). Therefore 1,1,2.-trichloroethane may be produced in landfills or other anaerobic environments (e.g., groundwater) that have been contaminated with 1,1,2,2-tetrachloroethane.

5.4 ENVIRONMENTAL FATE

5.4.1 Transport and Partitioning

Air. In the atmosphere, the dominant removal process is expected to be oxidation by photochemically-generated hydroxyl radicals, which proceeds by H-atom abstraction. Breakdown in both the air is slow. In the air, half the 1,1,2-trichloroethane is expected to breakdown in 49 days and therefore, it is likely to spread far from where it is released before breaking down.

Water. Based on a measured Henry's Law constant of $9.1x10^{-4}$ atm/m^3-mol (Ashworth et al. 1988), the volatilization half-life of 1,1,2-trichloroethane in a model river 1 m deep flowing 1 meter/second with a wind of 3 meters/second is estimated to be 4.5 hours, with resistance in the liquid phase primarily controlling volatilization (Thomas 1982). The half-life in a lake or pond would be much longer. The half-life of 1,1,2-trichloroethane in the lower Rhine river was 1.9 days (Zoeteman et al. 1980). This determination was based on monitoring data and river flow data. This half-life was ascribed to volatilization. In waste water treatment plants that receive refractory volatile compounds such as 1,1,2-trichloroethane from industrial discharges or other sources, stripping will be an important mechanism for transferring the chemical from the water into the air. In stripping, as opposed to ordinary volatilization, the liquid and gas phases are dispersed with the result that the interfacial surface area is much greater and liquid/gas mass transfer greatly enhanced. In five pilot scale treatment plants, 98–>99% of 1,1,2-trichloroethane was removed by this process (EPA 1981).

Sediment and Soil. In view of its moderately high vapor pressure and low adsorptivity to soil, 1,1,2-trichloroethane is expected to volatilize rapidly from soil surfaces. In one experiment in which 1,1,2-trichloroethane was applied to a column of sandy soil with a very low organic carbon content, volatilization and leaching were equally important transport processes (Thomas et al. 1982).

The adsorption based on organic carbon, K_{oc}, of 1,1,2-trichloroethane on a sandy forest soil (low organic carbon content and cation exchange capacity, CEC), an agricultural soil, and a forest soil (pH lower than the agricultural soil) was 60.0, 63.7, and 108, respectively (Seip et al. 1986). In soil column experiments

with these soils, the 1,1,2-trichloroethane moved through the sandy forest soil almost at the same rate as water, whereas the retardation was progressively greater in the agricultural soil and greatest in forest soil; the respective retention coefficients (velocity of water through the soil divided by the velocity of pollutant through the soil) being 1.53, 4.52, and 8.11 (Seip et al. 1986). Therefore 1,1,2-trichloroethane would not adsorb appreciably to soil, sediment, and suspended solids in the water column and would be expected to readily leach into the subsurface soil and groundwater. A second investigator obtained a K_{oc} of about 70 and a retardation factor of <1.5 using a sandy soil of lower organic carbon content than that used in the first study (Wilson et al. 1981).

Other Media. The bioconcentration factors (BCFs) for 1,1,2-trichloroethane reported in the literature are <10 (Kawasaki 1980) and 17 (Isnard and Lambert 1988). Therefore, it would not be expected to bioconcentrate in fish to any great extent.

5.4.2 Transformation and Degradation

Air. In the atmosphere, 1,1,2-trichloroethane will be degraded by reaction with photochemically-produced hydroxyl radicals. The reaction proceeds by H-atom abstraction to yield water and the corresponding $C_2H_2Cl_3$ radical. The rate of this reaction is $3.28x10^{-13}$ cc/molecules-second, which would give rise to a half-life of 49 days, assuming an average hydroxyl radical concentration of 5x10 radicals/cc (Jeong et al. 1984).

Water. 1,1,2-Trichloroethane undergoes both a pH-independent and a base-catalyzed hydrolysis at environmental pH. The neutral hydrolysis process is a substitution reaction leading to the formation of an alcohol, while the base-catalyzed reaction is an elimination reaction giving rise to 1,1-dichloroethene and HCl (Mabey et al. 1983; Vogel et al. 1987). In the case of 1,1,2-trichloroethane, the base-catalyzed rate is $5.9x10^{-3}$/mol-second at 25°C and is dominant above pH 5.4; the neutral rate is only $9x10^{-8}$ $seconds^{-1}$ at 80°C (Mabey et al. 1983). The half-life would be 37 years at pH 7 and 135 days at pH 9. This is consistent with observations that no significant decrease in concentration occurs in 8 days in sterilized water (Jensen and Rosenberg 1975). No significant degradation was obtained in seawater (pH 7.4–7.7) in 14 days at a temperature of 11–12°C (Jensen and Rosenberg 1975).

1,1,2-Trichloroethane showed no biodegradation in both a 24-day modified shake flask test and a river die-away test (Mudder and Musterman 1982). In two other biodegradation screening tests, one investigator reported no degradation and the other slow degradation after a long acclimation period

(Kawasaki 1980; Tabak et al. 1981). However the unknown extent to which volatilization contributed to losses in the second study makes the results suspect.

Under anaerobic conditions, 1,1,2-trichloroethane is reported to undergo dehalogenation. In order to establish whether this is a biologically mediated reaction and not simply an abiotic reaction catalyzed by free iron or iron porphyrin at low redox potential, Dow Chemical conducted 28-day studies in sterile solutions (Klecka and Gonsior 1983). They found that ppm concentrations of 1,1,2-trichloroethane did not undergo nonenzymatic dehalogenation in a sterile, anaerobic solution at pH 7 or when a sulfide redox buffer or hematin was added (Klecka and Gonsior 1983).

Sediment and Soil. The only study located regarding the degradation of 1,1,2-trichloroethane in soil involved subsurface samples taken from the margin of a floodplain near Lula, Oklahoma (Wilson et al. 1983). These samples were obtained both above the water table of a shallow aquifer and in the unconsolidated material in the saturated zone. A portion of the soil was sterilized and slurries were made and test chemical added. Manipulations made with samples from the saturated zone were carried out under nitrogen. After 16 weeks of incubation, no degradation of 1,1,2-trichloroethane was observed in the samples from above or below the water table. These results are in conflict with other studies (Wilson et al. 1983). It has been suggested that the time frame for the experiment may have been insufficient for resident microorganisms to have become acclimated to the chemical (Newsom 1985).

In an attempt to simulate the anaerobic conditions for biodegradation in landfills, experiments were performed under anoxic conditions using inocula from anaerobic digester units of waste water treatment facilities that were not acclimated to industrial solvents. After 1 week of incubation with 10 µg/L of 1,1,2-trichloroethane, 0.44 µg/g of vinyl chloride was formed, the highest level observed from any of the chlorinated ethanes or ethenes studied (Hallen et al. 1986). In further experiments when the concentration of inoculum was increased, 4.3 and 5.8 µg/g of vinyl chloride was formed after 1 and 2 weeks, respectively. The degradation reactions observed not only include reductive dehalogenation but the transformation of chlorinated ethanes into ethenes. It is interesting to note that autoclaved controls for a 1,1,2-trichloroethane anaerobic biodegradation experiment yielded 1,1-dichloroethene (Molton et al. 1987). The formation of 1,1-dichloroethene indicates that the conversion of 1,1,2-trichloroethane is nonbiological.

Degradation products (i.e., chloroethane, 1,2,dichloroethane, and vinyl chloride) were detected in 1,1,2-trichloroethane-amended microcosms constructed from anaerobic wetland sediments from the

Aberdeen Proving Ground, Maryland, but no chlorinated daughter products were found in abiotic (killed) 1,1,2-trichloroethane-amended microcosms (Lorah and Voytek 2004).

5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to 1,1,2-trichloroethane depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of 1,1,2-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 1,1,2-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 lowest limit of detections that are 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 Based on Standards[a]

Media	Detection limit	Reference
Air	<5 ppt	Grimsrud and Rasmussen 1975
Drinking water	0.2 µg/L	Comba and Kaiser 1983
Surface water and groundwater	0.2 µg/L	Comba and Kaiser 1983
Soil	0.2 µg/kg	EPA 1982b, 1986b
Sediment	5 µg/L	EPA 1987a
Whole blood	No data	Cramer et al. 1988

[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 1,1,2-Trichloroethane

Media	Low	High	For more information
Outdoor air (ppbv)	<LOD	0.011	Section 5.5.1
Indoor air (ppbv)	<LOD	2.5	Section 5.5.1
Surface water (ppm)	10	18	Section 5.5.2
Ground water (ppm)	1	350	Section 5.5.2

LOD = limit of detection

Detections of 1,1,2-trichloroethane in air, water, and soil at NPL sites are summarized in Table 5-6.

Table 5-6. 1,1,2-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)	39	77.2	51,900	83	55
Soil (ppb)	1,400	2,140	124,000	39	27
Air (ppbv)	3.3	15	41,700	15	11

[a]Concentrations found in ATSDR site documents from 1981 to 2017 for 1,854 NPL sites (ATSDR 2017). 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

Two air samples from rural Oklahoma and air samples from rural areas of the Pacific Northwest did not contain 1,1,2-trichloroethane (Brodzinsky and Singh 1982; Grimsrud and Rasmussen 1975). While both inland and nearshore rural sites near San Francisco averaged 14 ppt of 1,1,2-trichloroethane, 95% of inland sites and 46% of nearshore sites contained levels above the 6 ppt detection limit (Singh et al. 1977). In 930 urban/suburban sites in the United States, the 25th, 50th, 75th percentile and maximum concentrations of 1,1,2-trichloroethane were 0, 9.1, 22, and 11,000 ppt, respectively (Brodzinsky and Singh 1982). Other studies that include 13 major U.S. cities report average air concentrations of 1,1,2-trichloroethane ranging from 6 to 41 ppt (Harkov et al. 1983; Lioy et al. 1983; Singh et al. 1981, 1982). In the study by Harkov et al. (1983) air concentrations in Camden, Elizabeth, and Newark, New Jersey were monitored during the summer of 1981. Of the 111 samples measured, 27% contained a detectable quantity of the pollutant, with a detection limit of 5 ppt. The following winter, 41% of the samples from these cities contained 1,1,2-trichloroethane. The geometric mean concentrations ranged from 20 to 50 ppt for the winter measurements. This was significantly higher than the 10 ppt value obtained the previous summer (Harkov et al. 1987). The median concentration of 1,1,2-trichloroethane in 97 samples obtained from source-related areas throughout the United States was 45 ppt. Of these samples, 25% exceeded 210 ppt and a maximum concentration was 2,300 ppt was measured in Dominguez, California (Brodzinsky and Singh 1982). The data compiled by Brodzinsky and Singh (1982) have been reviewed and most of it is of good quality. More data have now been added to this National Ambient Volatile Organic Compounds Database bringing the number of monitoring data points to 886 (Shah and Heyerdahl 1988). According to this database, the median concentration of 1,1,2-trichloroethane in rural, suburban,

and urban areas was 0 ppt; at source-dominated sites, the median 1,1,2-trichloroethane concentration was 2 ppt. The limited monitoring data suggest that roughly one-quarter to one-half of the urban population may be exposed to the compound in air. Where 1,1,2-trichloroethane is found, most levels range from 10 to 50 ppt.

The only data on levels of 1,1,2-trichloroethane measured indoors were contained in a study of eight homes in Knoxville, Tennessee obtained during the winter (Gupta et al. 1984). Eleven of 16 samples contained 1,1,2-trichloroethane with a mean (standard deviation) concentration of 14.1 (7.8) μg/m^3 (2.5 [1.4] ppb); however, samples taken outside the homes did not contain detectable levels of the chemical. Sources of the 1,1,2-trichloroethane inside the homes may be building materials or solvent-containing products.

Traces to 0.32 ppb of 1,1,2-trichloroethane in air samples were found in Iberville Parish, Louisiana, where many organic chemical and producer, user, and storage facilities are located along the Mississippi River (Pellizarri 1982).

5.5.2 Water

1,1,2-Trichloroethane was not detected in composite samples of the water supplies of Philadelphia, Pennsylvania and Huntington, West Virginia, both of which are derived from surface sources (Dreisch et al. 1980). The levels in finished water from a New Orleans, Louisiana water supply ranged from 0.1 to 8.5 ppb (EPA 1980). In a 10-city EPA survey conducted in 1975, 1,1,2-trichloroethane was only detected in the water supply of Miami, Florida, which obtains its water from a groundwater source (EPA 1975). The level of contamination was not determined. The maximum concentration of 1,1,2-trichloroethane detected in a survey of community and noncommunity water supplies from groundwater sources and private wells in Suffolk County, New York, was 13 ppb (Zaki et al. 1986). 1,1,2-Trichloroethane has been found in 10 private wells in Rhode Island, at a concentration range of 1.0–14.0 ppb (RIDH 1989). A survey of Denver, Colorado, drinking water conducted in late 1985 to early 1986, found no 1,1,2-trichloroethane in the samples tested (Rogers et al. 198). In a U.S. Groundwater Supply survey, none of the 945 groundwater supply sources tested contained 1,1,2-trichloroethane at a quantitation limit of 0.5 ppb (Westrick et al. 1984). 1,1,2-Trichloroethane was found in 6 of the 1,174 community wells and 19 of the 617 private wells in a Wisconsin survey conducted in the early 1980s (Krill and Sonzogni 1986). All wells contained less than the recommended health advisory level of 6.1 ppb. Representative samples of groundwater and surface water were analyzed from the state of New Jersey during 1977–1979 (Page

1981). These samples were collected from every county, from urban, suburban, and rural areas, and from areas of every land use common in the state. Seventy-two of the 1,069 groundwater samples (6.7%) and 53 of the 603 surface water samples (8.7%) contained detectable levels of 1,1,2-trichloroethane with concentrations as high as 31.1 and 18.7 ppb being found for groundwater and surface water, respectively. Some of the most polluted wells were under urban land use areas (Greenberg et al. 1982; Page 1981). Groundwater near landfill sites in Minnesota and Wisconsin contained up to 31 ppb of 1,1,2-trichloroethane (Sabel and Clark 1984).

Of seven samples from two Ohio River tributaries, three were positive for 1,1,2-trichloroethane (0.6 ppb maximum). However, only 4% of the samples from the Ohio mainstream were positive and the compound was not found in 88 additional stations (Ohio River Valley Sanitation Commission 1980). One measurement of 1,1,2-trichloroethane in marine water was found, 153 ppt off the shore at Point Reyes, California (Singh et al. 1977).

Between 1980 and 1988, 3,255 samples of surface water in EPA's STORET database were analyzed for 1,1,2-trichloroethane (STORET 1988). Ten percent of the samples contained the chemical at ≥10 ppb. A maximum level of 18,000 ppb was reported in 1982. The maximum concentration of 1,1,2-trichloroethane reported for subsequent years ranged from 10 to 125 ppb. Of the 22,615 samples of groundwater in the database, 10% were >3 ppb. The maximum concentration of 1,1,2-trichloroethane in a groundwater was 350,000 ppb, reported in 1985. For the other years, the maximum concentration reported ranged from 18 to 1,800 ppb. Unfortunately, the detection limit is apparently recorded in STORET when no chemical is detected, so it is impossible to say whether the 90 percentile figure represents positive samples or merely higher detection limits.

5.5.3 Sediment and Soil

1,1,2-Trichloroethane was found in 25 of the 418 hazardous waste sites listed on the NPL of highest priority sites for possible remedial action (Mitre 1987). Additionally, it was found in three sites in the Contract Laboratory Statistical Database at mean concentrations ranging from 12 to 636 ppb (Viar and Company 1987).

5.5.4 Other Media

1,1,2-Trichloroethane was detected in 9 of 22 commercial batches of technical-grade 1,1,1-trichloroethane supplied by eight different European manufacturers and dealers (Henschler et al. 1980). The

concentration in these samples ranged from 300 to 3,015 ppm and the detection limit was 0.5 ppm. It was also found in some commercially available trichloroethylene in Japan (Tsuruta et al. 1983).

1,1,2-Trichloroethane was not detected in any of the 46 composite samples of human adipose tissue collected during FY82 as part of the National Human Adipose Tissue Survey (Stanley 1986). The composite specimens represented the nine U.S. census divisions stratified by three age groups (0–14, 15–44, and ≥45 years). Between July and December 1980, air and breath from nine New Jersey subjects were monitored in a pilot study to measure personal exposure to volatile organic substances for EPA's Total Exposure Assessment Methodology (TEAM) Study (Wallace et al. 1984). The personal air concentrations of 1,1,2-trichloroethane were below the detection limit in 151 of 161 of the samples; 7 contained trace levels of the chemical and the others ranged from 0.14 to 34.70 µg/m^3 (0.025–6.25 ppb), with a median of 0.35 µg/m^3 (0.063 ppb) (Wallace et al. 1984). Breath samples were negative in 44 of 49 samples and the others ranged from trace to 5.13 µg/m^3 (0.92 ppb), with a median of 0.2 µg/m^3 (0.036 ppb). No 1,1,2-trichloroethane was found in the subjects' drinking water at home.

5.6 GENERAL POPULATION EXPOSURE

Consistent with its tendency to partition into air, most exposures to 1,1,2-trichloroethane are from air. Limited environmental monitoring data suggest that one-quarter to one-half of the urban population may be exposed to the compound in air. Where 1,1,2-trichloroethane is found, levels appear to be about 10–50 ppt, for an average daily intake of 1.1–5.5 µg/day. It appears that the general population is rarely exposed to 1,1,2-trichloroethane in drinking water.

1,1,2-Trichloroethane levels have been monitored in blood samples from the 2003–2004, 2005–2006, 2007–2008, 2009–2010, and 2011–2012 NHANES. Blood levels were below the detection limit of 0.01 ng/mL in all surveys using participants’ whole blood sample (CDC 2017).

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

A NOES conducted by NIOSH from 1981 to 1983 estimates that 1,036 workers, including 15 women, were potentially exposed to 1,1,2-trichloroethane in the United States (NIOSH 1988). The estimate is provisional, as all of the data for trade name products which may contain 1,1,2-trichloroethane have not been analyzed. The NOES was based on field surveys of 4,490 facilities and was designed as a nationwide survey based on a statistical sample of virtually all workplace environments in the United States where eight or more persons are employed in all SIC codes except mining and agriculture. In the

earlier NIOSH National Occupational Hazard Survey, the highest exposures occurred around blast furnaces, in steel rolling mills, and in factories manufacturing technical instruments (Konietzko 1984).

If people use products containing 1,1,2-trichloroethane as a solvent, they will be potentially exposed to high levels of this chemical. Moolenaar and Olson (1989), in a written communication as spokesmen for the Dow Chemical Company, however, stated that they are not aware of any consumer uses and that the Dow Chemical Company screens potential customers to determine how they intend to use the 1,1,2-trichloroethane they purchase. Therefore, the potential for exposure from use of consumer products is probably low.

While it appears that exposure to high levels of 1,1,2-trichloroethane is rare, there are a few data that indicate that a small number of people may be exposed to high levels of 1,1,2-trichloroethane from contaminated air or drinking water. In Lake Charles, Louisiana, the median and maximum air concentrations of 1,1,2-trichloroethane were 4.8 and 7.4 ppb (Brodzinsky and Singh 1982). This indicates that half of the population of this community have a daily intake of 530–820 µg/g, compared with a median intake of 2.6 µg/g for all the urban/suburban areas of the United States that were monitored. Other cities where air concentrations >0.1 ppb were sometimes observed were Elizabeth, New Jersey; Deer Park, Texas; Freeport, Texas; Geismar, Louisiana; Edison, New Jersey, and Dominguez, California (Brodzinsky and Singh 1982). The data indicate that the air concentrations are variable, and only occasionally are high levels of 1,1,2-trichloroethane observed. From the available data, it is apparent that some wells in Suffolk County, New York, New Jersey, and near landfills in Minnesota and Wisconsin contain 1,1,2-trichloroethane concentrations as high as 13–31 ppb, corresponding to an average daily intake of 26–62 µg/g per day. The available data are insufficient to estimate the number of people that may be exposed to high levels of 1,1,2-trichloroethane.

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 1,1,2-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 1,1,2-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 Information on Health Effects

Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to 1,1,2-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 1,1,2-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.

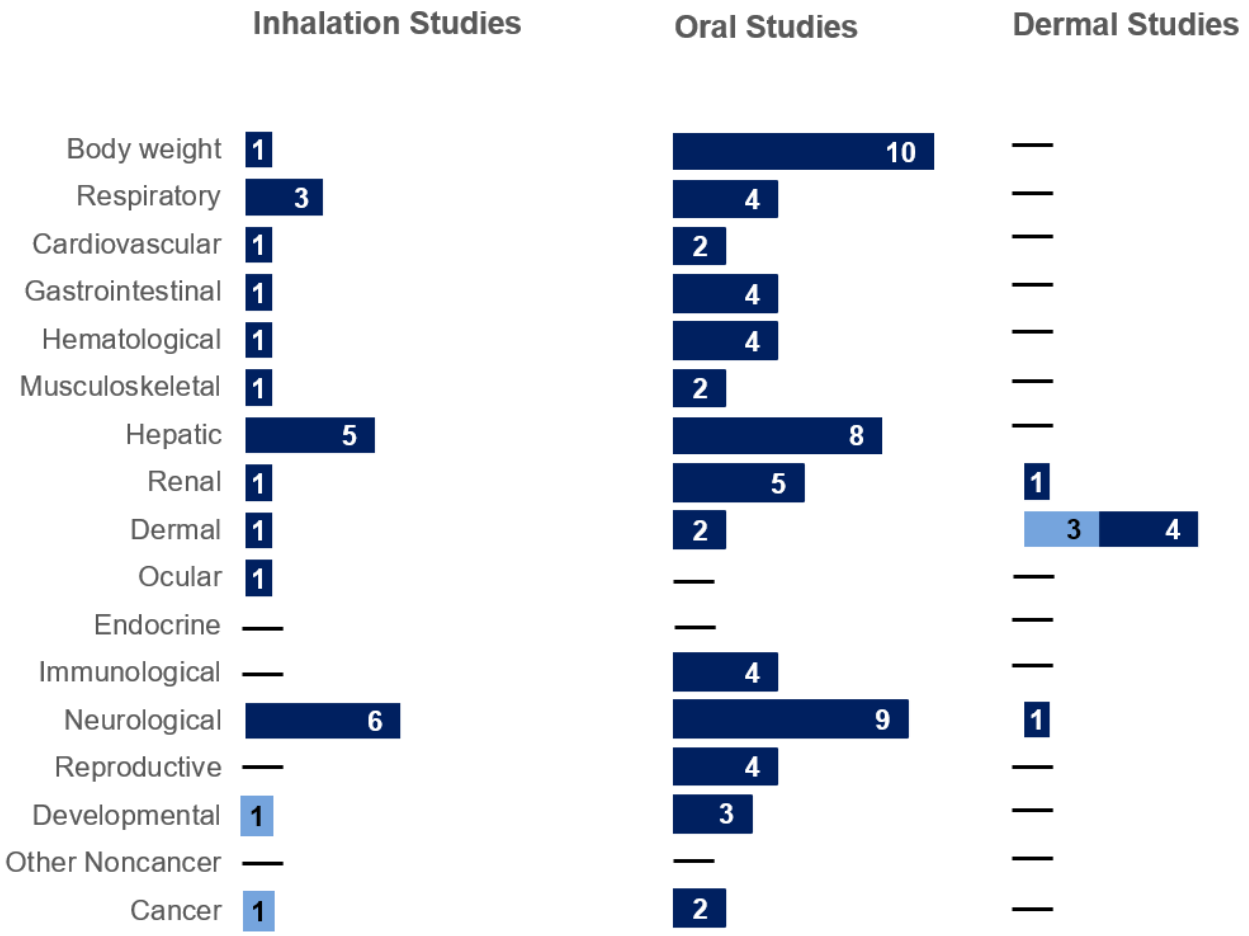
6.2 Identification of Data Needs

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 1989a), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to 1,1,2-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 1,1,2-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.

Figure 6-1. Summary of Existing Health Effects Studies on 1,1,2-Trichloroethane By Route and Endpoint[a]*

Potential body weight, liver, and neurological effects were the most studied endpoints
The majority of the studies examined oral exposure in **animals** (versus **humans**)



[a]Individual studies may have evaluated more than one of these endpoints.
*Includes studies discussed in Chapter 2; the number of studies include those finding no effect.

As illustrated in Figure 6-1, most of the data on the toxicity of 1,1,2-trichloroethane come from oral studies in laboratory animals. Five human studies were identified; three studies evaluated dermal endpoints and two epidemiology studies evaluated developmental or cancer endpoints. The most commonly examined endpoints in animal studies involving oral exposure were body weight, liver, and neurological. A smaller number of animal studies have assessed 1,1,2-trichloroethane toxicity following inhalation exposure; these studies primarily examined respiratory, hepatic, and neurological endpoints. Additionally, five animal dermal studies were identified; these studies examined a limited number of endpoints.

Acute-Duration MRLs. A number of single exposure studies have evaluated the toxicity of 1,1,2-trichloroethane following inhalation exposure. Based on these data, the most sensitive effect appears to be necrosis of the nasal olfactory epithelium in rats exposed to 58 ppm 1,1,2-trichloroethane for 4 hours (Kirkpatrick 2001). The study examined a wide range of endpoints and was considered suitable for derivation of a provisional MRL. Repeated exposure studies examining a wide range of potential endpoints including the nasal cavity and neurological endpoints are needed to establish concentration-response relationships. Acute-duration oral studies have identified several targets of toxicity in rats, mice, and dogs. The most sensitive endpoint appears to be hepatotoxicity. The available data were considered adequate for derivation of a provisional MRL. Additional studies, particularly studies evaluating repeated exposure, are needed to provide support for this MRL.

Intermediate-Duration MRLs. Although only one study examining the intermediate-duration inhalation toxicity of 1,1,2-trichloroethane (Kirkpatrick 2002) was located, the study examined a wide range of endpoints and was considered suitable for derivation of a provisional MRL. Additional studies that examined the nasal cavity and neurological endpoints (most sensitive target following oral exposure) would provide support this MRL. Intermediate-duration oral studies have examined a variety of potential endpoints in rats and mice; the data suggest that hepatotoxicity, immunotoxicity, and neurotoxicity are the most sensitive effects. An intermediate-duration oral MRL was derived based on hepatotoxicity and immunotoxicity endpoints. Since only one study evaluated immune function, additional immunotoxicity studies would provide support to the MRL.

Chronic-Duration MRLs. No chronic-duration inhalation studies were identified for 1,1,2-trichloro-ethane were identified and an MRL was not derived. The database was also considered inadequate for derivation of a chronic-duration oral MRL because no adverse effects, aside from lethality and cancer, were identified. Chronic inhalation and oral studies are needed. These studies should include a wide-

range of potential endpoints including the respiratory tract (inhalation studies), neurological endpoints, and immune function.

Health Effects. In addition to the inhalation and oral exposure studies identified in the discussion of MRL data needs, there is a need for dermal toxicity studies examining a wide range of potential endpoints. Toxicokinetic studies suggest that 1,1,2-trichloroethane can be absorbed through the skin (Jakobson et al. 1977; Kronevi et al. 1977) and studies are needed that would identify sensitive targets of toxicity and establish dose-response relationships.

Cancer Effects. A chronic-duration oral study (NCI 1978) reported increases in the occurrence of liver and adrenal tumors in mice exposed to 1,1,2-trichloroethane for 78 weeks; the study did not find increases in neoplastic lesions in similarly exposed rats. It is not known if a longer duration study would have also resulted in cancerous lesions in rats. Additionally, the carcinogenicity of 1,1,2-trichloroethane has not been evaluated following chronic inhalation or dermal exposure.

Immunotoxicity. The immunological effects of 1,1,2-trichloroethane have been studied following 14- and 90-day oral exposures. Several measures of both humoral and cell-mediated immune response were investigated in this study, and there was some indication that 1,1,2-trichloroethane elicited an immune response. The fact that effects were found in some tests, but not others intended to measure the same response, indicates that more studies of this type could provide worthwhile information. In addition, immune responses were different in male and female mice, and investigation of these differences might provide meaningful information. No studies were located regarding dermal sensitization by 1,1,2-trichloroethane.

Neurotoxicity. Studies of 1,1,2-trichloroethane in animals have provided information on the neurological effects produced by acute exposure to 1,1,2-trichloroethane, and the levels at which they occur. The results of one study suggested that taste aversion may be a sensitive indicator of the acute neurological effects of 1,1,2-trichloroethane. Additional neurobehavioral tests may reveal still more sensitive neurologic endpoints or provide support for use of taste aversion as an indicator of neurologic effects. Repeated exposure studies involved examination of neurological organs and tissues, but no tests of neurological function. Reliable studies of neurotoxicity by dermal exposure do not exist.

Epidemiology and Human Dosimetry Studies. There are limited epidemiology studies evaluating the toxicity or carcinogenicity of 1,1,2-trichloroethane (Brender et al. 2014; Dosemeci et al. 1999); common limitations of these studies are co-exposure to other pollutants and the lack of exposure data. In addition, experimental studies in humans have assessed dermal toxicity following short-term exposure. The evidence in animals, however, indicates that 1,1,2-trichloroethane can have effects on the nervous system, immune system, respiratory system, and liver and kidney function, and can be lethal. It is also carcinogenic in mice. These effects may also occur in humans, if they are exposed to appropriate levels of 1,1,2-trichloroethane. Epidemiological and human dosimetry studies might reveal whether humans are indeed susceptible to adverse health effects due to exposure to 1,1,2-trichloroethane.

Biomarkers of Exposure and Effect. Biomarkers do not adequately capture exposure to 1,1,2-trichloroethane. Although 1,1,2-trichloroethane and its metabolites can be measured in blood and urine, no studies have examined the possible relationship between potential biomarkers and exposure levels. No studies were located that identified biomarkers specific for 1,1,2-trichloroethane-induced effects. If epidemiological studies are performed that associate effects with exposure, it may be possible to identify alterations in blood chemistry indices or other pathological endpoints that would be useful to identify the disease state. Biomarkers for diagnosis of target organ toxicity (e.g., AST for liver damage) can provide useful information in conjunction with specific knowledge of 1,1,2-trichloroethane exposure.

Absorption, Distribution, Metabolism, and Excretion. Little information is available regarding the toxicokinetics of 1,1,2-trichloroethane in humans or animals. Information on absorption in humans comes from a brief study using two volunteers and from some studies in animals. Animal studies that specifically test the amount and rate of absorption of 1,1,2-trichloroethane would provide information as to how much 1,1,2-trichloroethane humans might be likely to absorb from various routes of exposure. For distribution, the only human data are from one briefly reported study; there are several acute-duration animal studies. More extensive and longer-term animal studies using the inhalation, oral, or dermal routes would help determine 1,1,2-trichloroethane distribution in the body. For metabolism, more animal studies would be helpful in showing what kind of metabolites might be expected to be found in the blood or urine of humans; if these could be measured, they might give an indication of amount of exposure to 1,1,2-trichloroethane. Additional metabolism studies may also reveal more definitive information on mechanisms of 1,1,2-trichloroethane toxicity and carcinogenicity. Data on excretion are fairly complete.

Comparative Toxicokinetics. No studies were located that compared human and animal toxicokinetics. Two comparative toxicokinetics studies were performed that examined the differences

between rats and mice in the types of metabolites formed, and the excretion rates from various routes. Although percent of administered dose metabolized was similar in both species, the overall rate of metabolism of 1,1,2-trichloroethane was greater in mice (Mitoma et al. 1985). The same metabolites were formed in the same proportions in both species. The difference in metabolic rate may be related to species differences in susceptibility to the toxic effects of 1,1,2-trichloroethane. More studies of this type could corroborate this theory or identify other factors that may be responsible for the species difference in toxicity.

Children's Susceptibility. There are limited data on children's susceptibility; the results of a 2-generation study suggest similar toxicity between immature and mature rats (Mylchreest 2006). However, additional animal studies are needed to examine potential differences in adults and children, particularly for more sensitive endpoints. Oral exposure studies do not suggest that 1,1,2-trichloroethane is a developmental toxicant. However, these studies did not examine potential effects on the development of the nervous system or immune system; studies in adult animals suggest that neurological and immunological endpoints are sensitive targets.

Physical and Chemical Properties. The physical and chemical properties of 1,1,2-trichloroethane have been adequately characterized (see Table 4-2).

Production, Import/Export, Use, Release, and Disposal. Data on current uses and disposal practices would be valuable in determining whether industrial activities pose an important source of human exposure to 1,1,2-trichloroethane.

Environmental Fate. Further investigation would resolve the discrepancies in the data for anaerobic degradation of 1,1,2-trichloroethane. Additional studies are needed to characterize the nature of the transformation and to clarify whether biotic, abiotic, or catalyzed abiotic reactions are involved and whether these reactions will generally occur under environmental conditions. A determination of the half-life in representative groundwater and sediment-water systems would be useful. From the available evidence, biodegradation in aerobic systems appears unlikely, although additional studies, particularly in soil, are desirable and would clarify this point.

Bioavailability from Environmental Media. Since 1,1,2-trichloroethane is expected to exist in the atmosphere as the vapor rather than adsorb to particulate matter, there would not be a competing adsorption that would impede its bioavailability via the lungs. Limited data showing the presence of

1,1,2-trichloroethane in adipose and other tissue of exposed subjects indicate that 1,1,2-trichloroethane is taken up via the lungs, gastrointestinal tract, or both. A pilot study demonstrated that similar low molecular weight chlorinated alkanes are found in human milk (Pellizzari et al. 1982). The source of these pollutants was probably ambient air, and this is the most probable route of intake for the general population.

Food Chain Bioaccumulation. 1,1,2-Trichloroethane has not been reported in food or biota, nor were any studies located in which the levels of this chemical in plants or animals were reported. The bioaccumulation potential for a chemical is most conveniently studied by measuring the BCF or the concentration of a chemical in fish divided by the concentration in water from which the chemical is taken up. The BCF of 1,1,2-trichloroethane in fish is reported to be <10 (Kawasaki 1980), indicating a very low potential for bioaccumulation in the food chain. Experimental verification of the lack of food chain bioaccumulation is not available. Such information can be obtained by studying the accumulation of 1,1,2-trichloroethane in organisms from different trophic levels that have been exposed to the chemical.

Exposure Levels in Environmental Media. The best estimates of exposure are based on monitoring data and these data add credence to emission and exposure estimates based on production and use. In the case of 1,1,2-trichloroethane, monitoring data are fragmentary and not very recent; most of the data are from the early 1980s or earlier. Information on production and use, particularly that with the largest probability for exposure, is not available. While 1,1,2-trichloroethane may be contained in some consumer products, the Dow Chemical Company is not aware of any consumer uses (Moolenaar and Olson 1989).

Exposure Levels in Humans. Estimates of general population and occupational exposure require current monitoring data or current data on production and use. This information is not available. The use pattern of 1,1,2-trichloroethane may have changed since the NOES. If this is the case, the results of the NOES could be reanalyzed in order to reflect current occupational exposures.

Exposures of Children. No studies are available to assess potential exposures of children.

6.3 Ongoing Studies

No ongoing studies were identified for 1,1,2-trichloroethane.

CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding 1,1,2-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 1,1,2-trichloroethane.

Table 7-1. Regulations and Guidelines Applicable to 1,1,2-Trichloroethane

Agency	Description	Information	Reference
	Air		
EPA	RfC	No data	IRIS 2003
WHO	Air quality guidelines	No data	WHO 2010
	Water & Food		
EPA	Drinking water standards and health advisories		EPA 2012
	1-Day health advisory (10-kg child)	0.6 mg/L	
	10-Day health advisory (10-kg child)	0.4 mg/L	
	DWEL	0.1 mg/L	
	Lifetime health advisory	0.003 mg/L	
	10^{-4} Cancer risk	0.06 mg/L	
	National primary drinking water regulations		EPA 2009b
	MCL	0.005 mg/L	
	PHG	0.003 mg/L	
	RfD	0.004 mg/kg/day	IRIS 2003
WHO	Drinking water quality guidelines	No data	WHO 2017
FDA	EAFUS	No data[a]	FDA 2013
	Level permissible in bottled water	0.005 mg/L	FDA 2017
	Cancer		
ACGIH	Carcinogenicity classification	A3[b]	ACGIH 2001
HHS	Carcinogenicity classification	No data	NTP 2016
EPA	Carcinogenicity classification	C[c]	IRIS 2003
IARC	Carcinogenicity classification	Group 3[d]	IARC 1999
	Occupational		
ACGIH	TLV (TWA)	10 ppm[e]	ACGIH 2001
OSHA	PEL (8-hour TWA) for general industry, shipyards and construction	10 ppm (45 mg/m^3)[f]	OSHA 2016a, 2016b, 2017

Table 7-1. Regulations and Guidelines Applicable to 1,1,2-Trichloroethane

Agency	Description	Information	Reference
NIOSH	REL (up to 10-hour TWA)	10 ppm (45 mg/m^3)[f,g]	NIOSH 2016
	IDLH	100 ppm[g]	NIOSH 1994
	Emergency Criteria		
EPA	AEGLs-air	No data	EPA 2016
DOE	PACs-air		DOE 2018b
	PAC-1[h]	30 ppm	
	PAC-2[h]	180 ppm	
	PAC-3[h]	500 ppm	

[a]The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.
[b]A3: confirmed animal carcinogen with unknown relevance in humans.
[c]Group C: possible human carcinogen.
[d]Group 3: not classifiable as to its carcinogenicity to humans.
[e]Skin notation.
[f]Skin designation.
[g]Potential occupational carcinogen.
[h]Definitions of PAC terminology are available from U.S. Department of Energy (DOE 2018a).

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; 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; GRAS = generally recognized as safe; 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; 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; PHG = public health goal; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit value; TWA = time-weighted average; WHO = World Health Organization

CHAPTER 8. REFERENCES

*ACGIH. 2001. Documentation of the threshold limit values and biological exposure indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienists.

ACGIH. 2010. 2010 TLVs and BEIs: Based on the documentation of the threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienists, 58, 73-74.

*Albano E, Tomasi A, Cheeseman KH, et al. 1985. Use of isolated hepatocytes for the detection of free radical intermediates of halogenated hydrocarbons. Free Radicals Liver Inj Proc Int Meet 1st, 7-16.

*Amin TA, Narang RS. 1985. Determination of volatile organics in sediment at nanogram-per-gram concentrations by gas chromatography. Anal Chem 57:648-651.

Anders MW, Jakobson I. 1985. Biotransformation of halogenated solvents. Scand J Work Environ Health 11(Suppl 1):23-32.

*Archer WL. 1979. Other chloroethanes. In: Kirk-Othmer encyclopedia of chemical technology. 3rd ed. 5:722-742.

Ashby J, Tennant RW. 1988. Chemical structure, Salmonella mutagenicity and extent of carcinogenicity as indicators of genotoxic carcinogenesis among 222 chemicals tested in rodents by the U.S. Mutat Res 204:17-115.

*Ashworth RA, Howe GB, Mullins ME, et al. 1988. Air-water partitioning coefficients of organics in dilute solutions. J Hazard Mater 18:25-36.

ATSDR. 1988. View Data Base. Atlanta, GA: Agency for Toxic Substances and Disease Registry, Office of External Affairs, Exposure and Disease Registry Branch.

*ATSDR. 1989a. Decision guide for identifying substance-specific data needs related to toxicological profiles; Notice. Fed Regist 54(174):37618-37634.

*ATSDR. 1989b. Toxicological profile for 1,1,2-trichloroethane. Agency for Toxic Substances and Disease Registry, U.S. Public Health Service. https://www.atsdr.cdc.gov/ToxProfiles/tp148.pdf. October 4, 2018.

*ATSDR. 2017. 1,1,2-Trichloroethane. Full SPL data. Substance priority list (SPL) resource page. Agency for Toxic Substances and Disease Registry, Centers for Disease Control and Prevention. http://www.atsdr.cdc.gov/SPL/resources/index.html. October 6, 2017.

*Barber ED, Donish WH. 1982. An exposure system for quantitative measurements of the microbial mutagenicity of volatile liquids. Environ Sci Res 25:3-18.Barber ED, Donish WH, Mueller KR. 1980. Quantitative measurement of the mutagenicity of volatile liquids in the Ames Salmonella/microsome assay [Abstract]. Environ Mutagen 2:307.

Barber ED, Donish WH, Mueller KR. 1981. A procedure for the quantitative measurement of the mutagenicity of volatile liquids in the Ames *Salmonella typhimurium* microsome assay. Mutat Res 90:31-48.

*Barkley J, Bunch J, Bursey JT, et al. 1980. Gas chromatography mass spectrometry computer analysis of volatile halogenated hydrocarbons in man and his environment: A multimedia environmental study. Biomed Mass Spectrom 7:139-147.

*Barnes DG, Dourson M. 1988. Reference dose (RfD): Description and use in health risk assessments. Regul Toxicol Pharmacol 8(4):471-486.

*Bauer U. 1981a. [Human exposure to environmental chemicals: Studies on volatile organic halogenated compounds in water, air, food and human tissues, III. Results of studies.] Zentralbl Bakteriol Mikrobiol Hyg Abt 1 Orig B 174:200-237. (German)

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* Cited in text

\+ Cited in supplemental document

8. REFERENCES

*Bauer U. 1981b. [Human exposure to environmental chemicals: Investigations on volatile organic halogenated compounds in water, air, food and human tissues: IV. Calculation of human exposure to organic halogenated compounds from the environment.] Zentralb Bakteriol Hyg Abt 1 Orig B 174:556-583. (German)

+*Beck MJ. 2004. An acute neurotoxicity study of 1,1,2-trichloroethane in rats. WIL Research Laboratories, Inc. EPA-HQ-OPPT-2002-0056-0100 through EPA-HQ-OPPT-2002-0056-0108. WIL-417004. https://www.regulations.gov/docketBrowser?rpp=25&so=DESC&sb=commentDueDate&po=0&dct=SR&D=EPA-HQ-OPPT-2002-0056. March 07, 2018.

*Bernauer U, Birner G, Dekant W, et al. 1996. Biotransformation of trichloroethene: dose-dependent excretion of 2,2,2-trichloro-metabolites and mercapturic acids in rats and humans after inhalation. Arch Toxicol 70(6):338-346.

Birnbaum LS. 1987. Age-related changes in carcinogen metabolism. J Am Geriatr Soc 35:51-60.

Bolt HM. 1987. Pharmacokinetic factors and their implications in the induction of mouse liver tumors by halogenated hydrocarbons. Arch Toxicol 10(Suppl 1):190-203.

+*Bonnet P, Francin JM, Gradiski D, et al. 1980. [Determination of the median lethal concentration of principle chlorinated aliphatic hydrocarbons in the rat.] Arch Mal Prof Med Trav Secur Soc 41:317-321. (French)

+*Borzelleca JF. 1983. A review of volatile organic contaminant data. Proc AWWA Water Qual Technol Conf 225:244.

*Bouwer EJ, McCarty PL. 1983. Transformation of 1- and 2-carbon halogenate aliphate organic compounds under methonorganic conditions. Appl Environ Microbial 45:1286-1294.

+*Brender JD, Shinde MU, Zhan FB, et al. 2014. Maternal residential proximity to chlorinated solvent emissions and birth defects in offspring: A case-control study. Environ Health 13:96. 10.1186/1476-069x-13-96.

*Brodzinsky R, Singh HB. 1982. Volatile organic chemicals in the atmosphere: An assessment of available data. SRI International, Atmospheric Science Center, Menlo Park, CA. Contract 68-02-3452, 98-99.

*Bronzetti G, Galli A, Vellosi R, et al. 1987. [Genetic activity of chlorinated ethanes.] Eur J Cancer Clin Oncol 23:1737-1738. (Italian)

+*Carlson GP. 1973. Effect of phenobarbital and 3-methylcholanthrene pretreatment on the hepatotoxicity of 1,1,1-trichloroethane and 1,1,2-trichloroethane. Life Sci 13:67-73.

+*Carpenter CP, Smyth HF, Jr, Pozzani UC. 1949. The assay of acute vapor toxicity, and the grading and interpretation of results on 96 chemical compounds. J Ind Hyg Toxicol 31:343-346.

*CAS. 1988. CA Registry File. Computer Printout.

*CDC. 2017. Fourth national report on human exposure to environmental chemicals. Updated tables, January 2017, Volume one. Atlanta, GA: Centers for Disease Control and Prevention, Department of Health and Human Services. https://www.cdc.gov/biomonitoring/pdf/FourthReport_UpdatedTables_Volume1_Jan2017.pdf. February 23, 2017.

*Chang LW, Pereira MA, Klaunig JE. 1985. Cytotoxicity of halogenated alkanes in primary cultures of rat hepatocytes from normal, partial hepatectomized and preneoplastic/neoplastic liver. Toxicol Appl Pharmacol 80:274-283.

*Clewell HJ, Andersen ME. 1985. Risk assessment extrapolations and physiological modeling. Toxicol Ind Health 1(4):111-131.

*Cole RH, Frederick RE, Healy RP, Roban RG. 1984. Preliminary findings of the priority pollutant monitoring project of the Nationwide Urban Runoff Program. J Water Pollut Control Fed 56(7):898-908.

*Comba ME, Kaiser KLE. 1983. Determination of volatile contaminants at the ng 1^{-1} level in water by capillary gas chromatography with electron capture detection. Int J Environ Anal Chem 16:17-31.

8. REFERENCES

*Cox RD. 1983. Sample collection and analytical techniques for volatile organics in air. Spec Conf Meas Monit Non-Criter (toxic) Contam Air, 101-112.

*Cramer PH, Boggess KE, Hosenfeld JM, et al. 1988. Determination of organic chemicals in human whole blood: Preliminary method development for volatile organics. Bull Environ Contam Toxicol 40:612-618.

*Crebelli R, Benigni R, Franekic J, et al. 1988. Induction of chromosome malsegregation by halogenated organic solvents in *Aspergillus nidulans*: Unspecific or specific mechanism? Mutat Res 201(2):401-411.

*Crebelli R, Carere A, Leopardi P, et al. 1999. Evaluation of 10 aliphatic halogenated hydrocarbons in the mouse bone marrow micronucleus test. Mutagenesis 14(2):207-215. http://mutage.oxfordjournals.org/cgi/content/abstract/14/2/207.

+*De Ceaurriz J, Bonnet P, Certin C, et al. 1981. [Chemicals as central nervous system depressants. Benefits of an animal model.] Cah Notes Doc 104:351-355. (French)

*DeMarini DM, Brooks HG. 1992. Induction of prophage lambda by chlorinated organics: Detection of some single-species/single-site carcinogens. Environ Mol Mutagen 19(2):98-111.

*DiRenzo AB, Gandolfi AJ, Sipes IG. 1982a. Microsomal bioactivation and covalent bonding of aliphatic halides to DNA. Toxicol Lett 11:243-253.

DiRenzo AB, Gandolfi AJ, Sipes IG, et al. 1982b. Effect of senescence on the bioactivation of aliphatic halides. Res Comm Chem Pathol Pharmacol 36:493-502.

DiRenzo AB, Gandolfi AJ, Sipes IG, et al. 1984. Effect of 0_2 tension on the bioactivation and metabolism of aliphatic halides by primary rat-hepatocyte cultures. Xenobiotica 14(7):521-525.

*Divincenzo GD, Krasavage WJ. 1974. Serum ornithine carbamyl transferase as a liver response test for exposure to organic solvents. Am Ind Hyg Assoc J 35:21-29.

*DOE. 2018a. Protective Action Criteria (PAC) with AEGLs, ERPGs, & TEELs: Rev. 29A, June 2018. Oak Ridge, TN: U.S. Department of Energy. https://sp.eota.energy.gov/pac/. July 26, 2018.

*DOE. 2018b. Table 3: Protective Action Criteria (PAC) Rev. 29a based on applicable 60-minute AEGLs, ERPGs, or TEELs. The chemicals are listed by CASRN. June 2018. Oak Ridge, TN: U.S. Department of Energy. https://sp.eota.energy.gov/pac/docs/Revision_29A_Table3.pdf. July 26, 2018.

*Doherty AT, Ellard S, Parry EM, et al. 1996. An investigation into the activation and deactivation of chlorinated hydrocarbons to genotoxins in metabolically competent human cells. Mutagenesis 11(3):247-274. http://mutage.oxfordjournals.org/cgi/content/abstract/11/3/247.

*Dosemeci M, Cocco P, Gomez M, et al. 1994. Effects of three features of a job exposure matrix on risk estimates. Epidemiology 5:124–127.

+*Dosemeci M, Cocco P, Chow WH. 1999. Gender differences in risk of renal cell carcinoma and occupational exposures to chlorinated aliphatic hydrocarbons. Am J Ind Med 36(1):54-59. http://www.ncbi.nlm.nih.gov/pubmed/10361587.

*Dreisch FA, Gower M, Munson TO. 1980. Survey of the Huntington and Philadelphia River water supplies for purgeable organic contaminants. Annapolis, MD: U.S. Environmental Protection Agency. EPA903981003.

*Driscoll JN, Duffy M, Pappas S, et al. 1987. Analysis of purgeable organics in water by capillary GC/PID-EICD. J Chromatogr Sci 25:369-375.

*Duprat P, Delsaut L, Gradiski D. 1976. [Irritating power of the principal aliphatic chloride solvents on the skin and ocular mucosa of the rabbit.] Eur J Toxicol Environ 9:171-177. (French)

Elovaara E, Hemminki K, Vainio H. 1979. Effects of methylene chloride, trichloroethane, trichloroethylene and toluene on the development of chick embryos. Toxicology 12:111-119.

*EPA. 1975. Preliminary assessment of suspected carcinogens in drinking water: Report to Congress. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances.

*EPA. 1980. Ambient water quality criteria for chlorinated ethanes. Washington, DC: U.S. Environmental Protection Agency, Office of Water Regulations and Standards. EPA440580029.

*EPA. 1981. Treatability manual. Washington, DC: U.S. Environmental Protection Agency. EPA60028200lA.

*EPA. 1982a. Methods for organic chemical analysis of municipal and industrial wastewater. Method Nos. 601 and 624. Cincinnati, OH: U.S. Environmental Protection Agency, Environmental Monitoring and Support Laboratory.

*EPA. 1982b. Test methods for evaluating solid waste. SW-846, 2nd ed. Physical/chemical methods. Method No. 5030. Washington, DC: U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response.

*EPA. 1982c. Fate of priority pollutants in publicly owned treatment works. Volume 1. U.S. Environmental Protection Agency. EPA440l82303, 35-44.

*EPA. 1986a. Methods for the determination of organic compounds in finished drinking water and raw source water. Method Nos. 502.1 and 524.2. Cincinnati, OH: U.S. Environmental Protection Agency, Physical and Chemical Methods Branch, Environmental Monitoring and Support Laboratory.

*EPA. 1986b. Test Methods for evaluating solid waste SW-846, 3rd ed., Vol. 1B: Laboratory manual: Physical/chemical methods. Washington, DC: U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response.

*EPA. 1986c. Hazardous States Environmental Protection Agency. Hazardous waste management system; identification and listing of hazardous waste. Fed Regist 51:6537-6537.

EPA. 1986d. Health effects assessment for 1,1,2-trichloroethane. Cincinnati, OH: U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office. PB86134566.

*EPA. 1987a. U.S. EPA Contract Laboratory Program Statement of Work for organic analysis. Washington, DC: U.S. Environmental Protection Agency.

*EPA. 1987b. Drinking water health advisory for 1,1,2-Trichloroethane. Draft. Washington, DC: U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office.

*EPA. 1987c. National primary drinking water regulations; synthetic organic chemicals; monitoring for unregulated contaminants. Fed Regist 52:25690-25717.

*EPA. 1988a. Integrated Risk Information System (IRIS). Risk estimate for carcinogenicity for 1,1,2-trichloroethane. Online. (Revised; Verification date 7/23/86). Cincinnati, OH: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office.

*EPA. 1988b. Analysis of Clean Water Act effluent guidelines pollutants. Summary of the chemicals regulated by industrial point source category. 40 CFR Parts 400-475. Draft. Washington, DC: U.S. Environmental Protection Agency, Office of Water Regulations and Standards.

*EPA. 1994. Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office. https://www.epa.gov/sites/production/files/2014-11/documents/rfc_methodology.pdf. October 3, 2018.

*EPA. 2005. Toxic chemical release inventory reporting forms and instructions: Revised 2004 version. Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986). U.S. Environmental Protection Agency, Office of Environmental Information. EPA260B05001.

*EPA. 2009a. 2009 Edition of the drinking water standards and health advisories. Washington, DC: U.S. Environmental Protection Agency. Office of Water. EPA822R09011. http://www.epa.gov/waterscience/criteria/drinking/dwstandards2009.pdf. May 19, 2010.

*EPA. 2009b. National primary drinking water regulations. Washington, DC: U.S. Environmental Protection Agency, Office of Ground Water and Drinking Water. EPA816F090004. https://www.epa.gov/sites/production/files/2016-06/documents/npwdr_complete_table.pdf. September 7, 2017.

8. REFERENCES

*EPA. 2012. Drinking water standards and health advisories. Washington, DC: U.S. Environmental Protection Agency, Office of Water. EPA822S12001. https://www.epa.gov/sites/production/files/2015-09/documents/dwstandards2012.pdf. April 25, 2013.

*EPA. 2016. Acute Exposure Guideline Levels (AEGLs) values. U.S. Environmental Protection Agency. https://www.epa.gov/sites/production/files/2016-03/documents/compiled_aegl_update_.pdf. September 8, 2017.

*FDA. 2013. Everything added to food in the United States (EAFUS). Washington, DC: U.S. Food and Drug Administration. http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting. January 8, 2014.

*FDA. 2017. Subpart B - Requirements for specific standardized beverages. Bottled water. Code of Federal Regulations. 21 CFR 165.110

Filser JG, Jurg P, Bolt HM. 1982. Decreased acetone exhalation induced by metabolites of halogenated C_1 and C_2 compounds. Arch Toxicol 49:107-116.

*Foureman P, Mason JM, Valencia R, et al. 1994. Chemical mutagenesis testing in Drosophila. IX. Results of 50 coded compounds tested for the National Toxicology Program. Environ Mol Mutagen 23(1):51-63. http://www.ncbi.nlm.nih.gov/pubmed/8125083.

Gandolfi AJ, Van Dyke RA. 1973. Dechlorination of chloroethane with a reconstituted liver microsomal system. Biochem Biophys Res Commun 53:687-692.

Gargas ML, Burgess RJ, Voisard DE, et al. 1989. Partition coefficients of low-molecular-weight volatile chemicals in various liquids and tissues. Toxicol Appl Pharmacol 98:87-99.

+*Gehring PJ. 1968. Hepatotoxic potency of various chlorinated hydrocarbon vapours relative to their narcotic and lethal potencies in mice. Toxicol Appl Pharmacol 13:287-298.

Ghittori S, Imbriani M, Pezzagno G, et al. 1987. The urinary concentration of solvents as a biological indicator of exposure: Proposal for the biological equivalent exposure limit for nine solvents. Am Ind Hyg Assoc J 48:786-790.

*Gold LS, Backman GM, Hooper NK, et al. 1987. Ranking the potential carcinogenic hazards to workers from exposures to chemicals that are tumorigenic in rodents. Environ Health Perspect 76:211-219.

Gold LS, Ward JM, Bernstein L, et al. 1986. Association between carcinogenic potency and tumor pathology in rodent carcinogenesis bioassays. Fundam Appl Toxicol 6:677-690.

+*Gradiski D, Bonnet P, Raoult G, et al. 1978. [Comparative acute inhalation toxicity of the principal chlorinated aliphatic solvents.] Arch Mal Prof Med Trav Secur Soc 39:249-257. (French)

Grasso P. 1982. Carcinogenicity of solvents. In: Collings AJ, Luxon SG, eds. Safe use of solvents. London, England: Academic Press, Inc., 129-136.

*Green T, Dow J, Ellis MK, et al. 1997. The role of glutathione conjugation in the development of kidney tumours in rats exposed to trichloroethylene. Chem Biol Interact 105(2):99-117.

*Greenberg M, Anderson R, Keene J, et al. 1982. Empirical test of the association between gross contamination of wells with toxic substances and surrounding land use. Environ Sci Technol 16:14-19.

*Grimsrud EP, Rasmussen RA. 1975. Survey and analysis of halocarbons in the atmosphere by gas chromatography-mass spectrometry. Atmos Environ 9:1014-1017.

*Gupta KC, Ulsamen AG, Gammage R. 1984. Volatile organic compounds in residential air: Levels, sources and toxicity. Presented at the 77th Annual Meeting Air Pollution Control Association, San Francisco, CA. June 24-29.

Hales DB, Thompson JA. 1985. Kinetic and mechanistic studies of the cytochrome P-450 catalyzed oxidation of chloroethanes. (Abstract) Fed Proc 44:1259.

*Hallen RT, Pyne JW, Molton PM. 1986. Transformation of chlorinated ethenes and ethanes by anaerobic microorganisms. (Abstract). Presented before the Division of Environmental Chemistry, American Chemical Society. 192nd Annual Meeting, Anaheim, CA. September 7-12, 1986, 344-346.

8. REFERENCES

*Hanasono GK, Witschi H, Plaa GL. 1975. Potentiation of the hepatotoxic responses to chemicals in alloxan-diabetic rats. Proc Soc Exp Biol Med 149:903-907.

*Harkov R, Gianti SJ Jr, Bozzelli JW, et al. 1985. Monitoring volatile organic compounds at hazardous and sanitary landfills in New Jersey (USA). J Environ Sci Health Part A Environ Sci Eng 20:491-502.

*Harkov R, Kebbekus B, Bozzelli JW, et al. 1983. Measurement of selected volatile organic compounds at three locations in New Jersey during the summer season. J Air Pollut Control Assoc 33:1177-1183.

*Harkov R, Kebbekus B, Bozzelli JW. 1987. Volatile organic compounds at urban sites in New Jersey. In: Lioy PJ, Daisey JM, eds. Toxic air pollutants. Chelsea, MI: Lewis Publishers Inc., 69-88.

*Harms MS, Peterson RE, Fujimoto JM, et al. 1976. Increased "bile duct pancreatic fluid" flow in chlorinated hydrocarbon-treated rats. Toxicol Appl Pharmacol 35:41-49.

Hathway DE. 1981. Foreign compound metabolism in mammals. Vol 6. A review of literature published during 1978 and 1979. London, England: Royal Society of Chemistry, 160-197.

*Hawley. 1981. Condensed chemical dictionary. 10th ed., 1041.

Helmes CT, Atkinson DL, Sigman CC, et al. 1982. Evaluation and classification of the potential carcinogenicity of organic air pollutants. J Environ Sci Health 17(Part A):321-390.

*Henschler D, Reichert D, Metzler M. 1980. Identification of potential carcinogens in technical grade 1,1,1-trichloroethane. Int Arch Occup Environ Health 47:263-268.

*Hiatt MH. 1981. Analysis of fish and sediment for volatile priority pollutants. Anal Chem 53:1541-1543.

*Hiatt MH. 1983. Determination of volatile organic compounds in fish samples by vacuum distillation and fused silica capillary gas chromatography/mass spectrometry. Anal Chem 55:506-516.

Holmberg B, Malmfors T. 1974. Cytotoxicity of some organic solvents. Environ Res 7:183-192.

*IARC. 1979. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Vol 20. Some halogenated hydrocarbons. Lyon, France: International Agency for Research on Cancer.

*IARC. 1999. 1,1,2-Trichloroethane. IARC Monographs on the evaluation of carcinogenic risks to humans. Volume 71. Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide. Lyon, France: International Agency for Research on Cancer. http://monographs.iarc.fr/ENG/Monographs/vol71/mono71-55.pdf. November 21, 2017.

*Ikeda M, Ohtsuji H. 1972. A comparative study of the excretion of Fujiwara reaction-positive substances in urine of humans and rodent given trichloro- or tetrachloro-derivatives of ethane and ethylene. Br J Ind Med I 29:99-104.

Imbriani M, Ghittori S, Pezzagno G, et al. 1985. Urine/air partition coefficient for some industrially important substances. G Ital Med Lav 7:133-140.

*IOM. 2010. Summary. In: Micheel CM, Ball JR, eds. Evaluation of biomarkers and surrogate endpoints in chronic disease. Washington, DC: The National Academies Press, 1-16. http://doi.org/10.17226/12869.

*IRIS. 2003. 1,1,2-Trichloroethane. Integrated Risk Information System. Chemical assessment summary. Washington, DC: U.S. Environmental Protection Agency. https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0198_summary.pdf. November 21, 2017.

*Isnard P, Lambert S. 1988. Estimated bioconcentration factors from octanol-water partition coefficient and aqueous solubility. Chemosphere 17:21-34.

*Ivanetich KM, Van Den Honert LH. 1981. Chloroethanes: Their metabolism by hepatic cytochrome P-450 *in vitro*. Carcinogenesis 2:697-702.

*Jackson DR, Garrett BC, Bishop TA. 1984. Comparison of batch and column methods for assessing leachability of hazardous waste. Environ Sci Technol 18:668-673.

8. REFERENCES

*Jakobson I, Holmberg B Wahlberg JE. 1977. Variations in the blood concentration of 1,1,2-trichloroethane by percutaneous absorption and other routes of administration in the guinea pig. Acta Pharmacol Toxicol 41:497-506.

*Jensen S, Rosenberg R. 1975. Degradability of some chlorinated aliphatic hydrocarbons in sea water and sterilized water. Water Res 9:659-661.

*Jeong KM, Hsu KJ, Jeffries JB, et al. 1984. Kinetics of the reactions of hydroxyl with ethane, 1,1,1-trichloroethane, 1,1,2-trichloroethane, 1,1difluoro-1,2-dichloroethane, and 1,1,1,2-tetrafluoroethane. J Phys Chem 88:1222-1226.

*Jernigan JD, Pounds JG, Harbison RD. 1983. Potentiation of chlorinated hydrocarbon toxicity by 2,5-hexanedione in primary cultures of adult rat hepatocytes. Fundam Appl Toxicol 3:22-26.

*Kaiser KLE, Comba ME. 1986. Volatile halocarbon contaminant survey of the St. Clair River. Water Pollut Res J Can 21:323-331.

+*Kallman MJ, Kaempf GL. 1984. Efficacy of choice testing to predict chronic ingestion of drinking solutions adulterated with chemicals. Pharmacol Biochem Behav 20:195-200.

+*Kallman MJ, Lynch MR, Landauer MR. 1983. Taste aversions to several halogenated hydrocarbons. Neurobehav Toxicol Teratol 5:23-27.

*Kawasaki M. 1980. Experiences with the test scheme under the chemical control law of Japan: An approach to structure-activity correlations. Ecotoxicol Environ Saf 4:444-454.

*Kebbekus BB, Bozzelli JW. 1982. Collection and analysis of selected volatile organic compounds in ambient air. Proc Ann Meet Air Pollut Control Assoc 75:82-65.2, 15 p.

*King L, Sherbin G. 1986. Point sources of toxic organics to the upper St. Clair River. Water Pollut Res J Canada 21:433-446.

+*Kirkpatrick DT. 2001. Acute inhalation toxicity (with histopathology) study of 1,1,2-trichloroethane (1,1,2-TCE) in rats. WIL Research Laboratories, Inc. HAP Task Force. EPA-HQ-OPPT-2002-0056-0039. WIL-417001. https://www.regulations.gov/document?D=EPA-HQ-OPPT-2002-0056-0039. March 07, 2018.

+*Kirkpatrick DT. 2002. A 90-day inhalation toxicity study of 1,1,2-trichloroethane (1,1,2-TCE) in rats (with satellite groups for pharmacokinetic evaluations in rats and mice). WIL Research Laboratories, Inc. HAP Task Force. EPA-HQ-OPPT-2002-0046-0003. WIL-417002. https://www.regulations.gov/document?D=EPA-HQ-OPPT-2002-0046-0003. March 07, 2018.

*Klaassen CD, Plaa GL. 1966. Relative effects of various chlorinated hydrocarbons on liver and kidney function in mice. Toxicol Appl Pharmacol 9:139-151.

*Klaassen CD, Plaa GL. 1967a. Relative effects of various chlorinated hydrocarbons on liver and kidney function in dogs. Toxicol Appl Pharmacol 10:119-131.

*Klaassen CD, Plaa GL. 1967b. Susceptibility of male and female mice to the nephrotoxic and hepatotoxic properties of chlorinated hydrocarbons. Proc Soc Exp Biol Med 124:1163-1166.

*Klaassen CD, Plaa GL. 1969. Comparison of the biochemical alterations elicited in livers from rats treated with carbon tetrachloride, chloroform, 1,1,2-trichloroethane and 1,1,1-trichloroethane. Biochem Pharmacol 18:2019-2027.

*Klecka GM, Gonsior SJ. 1983. Nonenzymatic reductive dechlorination of chlorinated methanes and ethanes in aqueous solution. Report ES-645. Dow Chemical USA Environmental Research Lab.

*Kluwe WM, Herrmann CL, Hook JB. 1979. Effects of dietary polychlorinated biphenyls and polybrominated biphenyls on the renal and hepatic toxicities of several chlorinated hydrocarbon solvents in mice. J Toxicol Environ Health 5:605-616.

*Kluwe WM, McCormack KM, Hook JB. 1978. Potentiation of hepatic and renal toxicity of various compounds by prior exposure to polybrominated biphenyls. Environ Health Perspect 23:241-246.

*Konietzko H. 1984. Chlorinated ethanes: Sources, distribution, environmental impact and health effects. Hazard Assess Chem: Curr Dev 3:401-448.

*Krill RM, Sonzogni WC. 1986. Chemical monitoring of Wisconsin's groundwater. J Am Water Works Assoc 78:70-75.

*Krishnan K, Anderson ME, Clewell HJ, et al. 1994. Physiologically based pharmacokinetic modeling of chemical mixtures. In: Yang RSH, ed. Toxicology of chemical mixtures. Case studies, mechanisms, and novel approaches. San Diego, CA: Academic Press, 399-437.

+*Kronevi T, Wahlberg J, Holmberg B. 1977. Morphological lesions in guinea pigs during skin exposure to 1,1,2-trichloroethane. Acta Pharmacol Toxicol 41:298-305.

*LaRegina J, Bozzelli JW, Harkov R, et al. 1986. Volatile organic compounds at hazardous waste sites and a sanitary landfill in New Jersey. Environ Prog 8:18-26.

+*Lazarew NW. 1929. Uber die narkotsche Wirkungskraft der Dampfe der chlorderivaten des methans, des Athans und des Anthylens. Arch Exp Pathol Pharmacol 141:19-24.

*Liepins R, Mixon F, Hudak C, et al. 1977. Industrial process profile for environmental use: Chapter 6. Cincinnati, OH: U.S. Environmental Protection Agency, Office of Research and Development, Industrial Environmental Research Laboratory. EPA600277023f. PB281478.

*Lioy PJ, Atherholt T, Bozzelli J, et al. 1983. The New Jersey project on Airborne Toxic Elements and Organic Substances (ATEOS): A summary of the 1981 summer and 1982 winter studies. J Water Pollut Control Fed 33:649-657.

Lipsky MM. 1984. A brief review of the toxicity and carcinogenicity of select chlorinated hydrocarbons. Adv Mod Environ Toxicol 7:141-151.

*Little AD. 1983. Cell transformation assays of 11 chlorinated hydrocarbon analogs (Final Report) ICAIR work assignment No. 10. EPA/OTS Document #40-8324457.

*Lopez-Avila V, Heath N, Hu A. 1987. Determination of purgeable halocarbons and aromatics by photoionization and hall electrolytic conductivity detectors connected in series. J Chromatogr Sci 25:356-363.

*Lorah MM, Voytek MA. 2004. Degradation of 1,1,2,2-tetrachloroethane and accumulation of vinyl chloride in wetland sediment microcosms and in situ porewater: Biogeochemical controls and associations with microbial communities. J Contam Hydrol 70(1-2):117-145. http://www.ncbi.nlm.nih.gov/pubmed/15068871.

*Lundberg I, Ekdahl M, Kronevi T, et al. 1986. Relative hepatotoxicity of some industrial solvents after intraperitoneal injection or inhalation exposure in rats. Environ Res 40:411-420.

*Mabey WR, Barich V, Mill T. 1983. Hydrolysis of polychlorinated alkanes. In: Symp Amer Chem Soc Div Environ Chem 186th Natl Mtg, Washington, DC. 23:359-361.

MacDonald JR, Gandolfi AJ, Sipes IG. 1980. Potentiation of 1,1,2-trichloroethane hepatotoxicity by acetone pre-treatment. Fed Proc 39:999.

*MacDonald JR, Gandolfi AJ, Sipes IG. 1982. Acetone potentiation of 1,1,2-trichloroethane hepatotoxicity. Toxicol Lett 13:57-69.

Maiorino RM, Gandolfi AJ, Brendel K, et al. 1982. Chromatographic resolution of amino acid adducts of aliphatic halides. Chem Biol Interact 38:175-188.

+*Maurissen JP, Andrus AK, Johnson KA, et al. 2005. 1,1,2-Trichloroethane: Subchronic neurotoxicity study in F344/DUCRL rats. Parts 1-4. Dow Chemical Company. EPA-HQ-OPPT-2002-0046-0013 through EPA-HQ-OPPT-2002-0046-0016. Study Id: 041056. https://www.regulations.gov/docketBrowser?rpp=25&so=DESC&sb=commentDueDate&po=0&dct=SR&D=EPA-HQ-OPPT-2002-0046. March 07, 2018.

*Mazzullo M, Colacci A, Grilli S, et al. 1986. 1,1,2-Trichloroethane: Evidence of genotoxicity from short-term tests. Jpn J Cancer Res 77:532-539.

*Mersch-Sundermann et al. 1989. Examination of mutagenicity of organic microcontaminations of the environment: Communication IV. The mutagenicity of halogenated aliphatic hydrocarbons with the SOS-Chromotest. Zentralbl Hyg Umweltmed 189(3):266-271.

*Michael LC, Erickson MD, Parks SP, et al. 1980. Volatile environmental pollutants in biological matrices with a headspace purge technique. Anal Chem 52:1836-1841.

*Milman HA, Mitoma C, Tyson C, et al. 1984. Comparative pharmacokinetics/ metabolism, carcinogenicity and mutagenicity of chlorinated ethanes and ethylenes (Meeting abstract). International Conf on Organic Solvent Toxicity, October 15-17, 1984.

8. REFERENCES

*Milman HA, Story DL, Riccio ES, et al. 1988. Rat liver foci and *in vitro* assays to detect initiating and promoting effects of chlorinated ethanes and ethylenes. Ann N Y Acad Sci 534:521-530. http://www.ncbi.nlm.nih.gov/pubmed/3389679.

*Mirsalis JC, Tyson CK, Steinmetz KL, et al. 1989. Measurement of unscheduled DNA synthesis and S-phase synthesis in rodent hepatocytes following *in vivo* treatment: Testing of 24 compounds. Environ Mol Mutagen 14(3):155-164. http://www.ncbi.nlm.nih.gov/pubmed/2792091.

*Mitoma C, Tyson CA, Riccio ES. 1985. Investigation of the species sensitivity and mechanism of carcinogenicity of halogenated hydro- carbons final report EPA Contract 68-01-5079. EPA/OTS; Document #40-842-8424225.

*Mitre. 1987. National priority list technical database. McLean, VA: The Mitre Corp.

*Miyagawa M, Takasawa H, Sugiyama A, et al. 1995. The *in vivo-in vitro* replicative DNA synthesis (RDS) test with hepatocytes prepared from male B6C3F1 mice as an early prediction assay for putative nongenotoxic (Ames-negative) mouse hepatocarcinogens. Mutat Res 343(2-3):157-183.

*Molton PM, Hallen RT, Pyne JW. 1987. Study of vinyl chloride formation at landfill sites in California. Report BNWL-2311206978. Richland, WA: Battelle Pacific Northwest Laboratories. PB87161278.

+*Moody DE, Smuckler EA. 1986. Disturbances in hepatic heme metabolism in rats administered alkyl halides. Toxicol Lett 32:209-214.

+*Moody DE, James JL, Clawson GA, et al. 1981. Correlations among the changes in hepatic microsomal components after intoxication with alkyl halides and other hepatotoxins. Mol Pharmacol 20:685-693.

*Moolenaar RJ and Olson RD. 1989. Written communication. Comments of the Dow Chemical Company on ATSDR's Toxicological Profile for 1,1,2-Trichloroethane. Dow Chemical Company, Midland, MI. (May 12).

*Morgan A, Black A, Belcher DR. 1970. The excretion in breath of some aliphatic halogenated hydrocarbons following administration by inhalation. Ann Occup Hyg 13:219-233.

*Morgan A, Black A, Belcher DR. 1972. Studies on the absorption of halogenated hydrocarbons and their excretion in breath using ^{38}Cl tracer techniques. Ann Occup Hyg 15:273-282.

*Morgan KT. 1991. Approaches to the identification and recording of nasal lesions in toxicology studies. Toxicol Pathol 19(4 Pt 1):337-351.

*Mosesman NH, Sidisky IM, Corman SD. 1987. Factors influencing capillary analysis of volatile pollutants. J Chromatogr Sci 25:351-355.

*Mudder TI, Musterman JL. 1982. Development of empirical structure biodegradability relationships and biodegradability testing protocol for volatile and slightly soluble priority pollutants. Presented before the Div Environ Chem Amer Chem Soc, Kansas City, MO. September 1982, 52-53.

+*Mylchreest E. 2006. 1,1,2-Trichloroethane: Multigeneration reproduction study in rats. Volume 1-5. E.I. du Pont de Nemours and Company. HAP Task Force. EPA-HQ-OPPT-2002-0056-0127. DuPont-16013. https://www.regulations.gov/document?D=EPA-HQ-OPPT-2002-0056-0127.

Nakajima T, Sato A. 1979. Enhanced activity of liver drug-metabolizing enzymes for aromatic hydrocarbons and chlorinated hydrocarbons following food deprivation. Toxicol Appl Pharmacol 50:549-556.

*NAS. 2009. Systemic exposures to volatile organic compounds and factors influencing susceptibility to their effects. In: Contaminated water supplies at Camp Lejeune: Assessing potential health effects. Washington, DC: National Research Council, 74-78.

*NAS/NRC. 1989. Report of the oversight committee. Biologic markers in reproductive toxicology. Washington, DC: National Academy of Sciences, National Research Council, National Academy Press, 15-35.

*NATICH. 1987. NATICH data base report in state, local and EPA air toxics activities. National Air Toxics Information Clearinghouse. OAQPS. Research Triangle Park, NC: State and Territorial Pollution Program. Administrators Association of Local Air Pollution. Central Officials.

8. REFERENCES

+*NCI. 1978. Bioassay of 1,1,2-trichloroethane for possible carcinogenicity. ISS DHEW/PUB/NIH-78-1324. NCI-CG-TR-74. PB283337.

*Newsom JM. 1985. Transport of organic compounds dissolved in ground water. Ground Water Monit Rev 5:28-36.

+*Niklasson M, Tham R, Larsby B, et al. 1993. Effects of toluene, styrene, trichloroethylene, and trichloroethane on the vestibule- and opto-oculo motor system in rats. Neurotoxicol Teratol 15(5):327-334.

NIOSH. 1977a. NIOSH manual of analytical methods. 2nd ed., Vol. 1, Method No. P&CAM 127. Cincinnati, OH: U.S. Department of Health Education and Welfare, Center for Disease Control, NIOSH.

NIOSH. 1977b. NIOSH manual for analytical methods. 2nd ed., Vol. 2, Method No. 5134. Cincinnati, OH: U.S. Department of Health Education and Welfare, Center for Disease Control.

NIOSH. 1985. Current intelligence bulletin 27. Chloroethanes: Review of Toxicity. Cincinnati, OH: National Institute for Occupational Safety and Health. PB85119196.

*NIOSH. 1988. National Institute for Occupational Safety and Health. National Occupational Exposure Survey (NOES). Computer Printout 10/20/88.

*NIOSH. 1994. 1,1,2-Trichloroethane. Immediately Dangerous to Life or Health Concentrations (IDLH). Atlanta, GA: National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention. https://www.cdc.gov/niosh/idlh/79005.html. November 21, 2017.

*NIOSH. 2016. 1,1,2-Trichloroethane. NIOSH pocket guide to chemical hazards. Atlanta, GA: National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention. https://www.cdc.gov/niosh/npg/npgd0628.html. November 21, 2017.

*NLM. 1988. Hazardous Substance Data Bank. Bethesda, MD: National Library of Medicine. National Institutes of Health.

*Norpoth K, Heger M, Muller G, et al. 1988. Investigations on metabolism and carcinogenicity of 1,1,2-trichloroethane. J Cancer Res Clin Oncol 114:158-162.

*NTP. 2005. Report on carcinogens, eleventh edition. Research Triangle Park, NC: U.S. Department of Health and Human Services. Public Health Service. National Toxicology Program. http://ntpserver.niehs.nih.gov/ntp/roc/toc11.html. July 31, 2008.

*NTP. 2013. Draft OHAT approach for systematic review and evidence integration for literature-based health assessments- February 2013. National Toxicology Program. U.S. Department of Health and Human Services, Office of Health Assessment and Translation. https://ntp.niehs.nih.gov/ntp/ohat/evaluationprocess/draftohatapproach_february2013.pdf. October 4, 2018.

*NTP. 2015. Handbook for conducting a literature-based health assessment using OHAT approach for systematic review and evidence integration. National Toxicology Program. U.S. Department of Health and Human Services, Office of Health Assessment and Translation. https://ntp.niehs.nih.gov/ntp/ohat/pubs/handbookjan2015_508.pdf. October 4, 2018.

*NTP. 2016. Report on carcinogens, Fourteenth edition. CASRN Index in MS Excel. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program. https://ntp.niehs.nih.gov/pubhealth/roc/index-1.html#P. March 1, 2017.

*Ohio River Valley Sanitation Commission. 1980. Assessment of water quality conditions. Ohio River Mainstream 1978-79. Cincinnati, OH.

OSHA. 1989. Air contaminants: Final rule. U.S. Department of Labor. Occupational Safety and Health Administration. 29 CFR 1910.1000. Fed Regist 54(12):2332-2960.

*OSHA. 2016a. Subpart D - Occupational health and environment controls. Gases, vapors, fumes, dusts, and mists. Code of Federal Regulations. 29 CFR 1926.55. Occupational Safety and Health Standards. https://www.gpo.gov/fdsys/pkg/CFR-2016-title29-vol8/pdf/CFR-2016-title29-vol8-sec1926-55.pdf. March 6, 2017.

8. REFERENCES

*OSHA. 2016b. Subpart Z - Toxic and hazardous substances. Air contaminants. Code of Federal Regulations. 29 CFR 1910.1000. Occupational Safety and Health Standards. https://www.gpo.gov/fdsys/pkg/CFR-2016-title29-vol6/pdf/CFR-2016-title29-vol6-sec1910-1000.pdf. March 6, 2017.

*OSHA. 2017. Subpart Z - Toxic and hazardous substances. Air contaminants. Code of Federal Regulations. 29 CFR 1915.1000. Occupational Safety and Health Standards. https://www.gpo.gov/fdsys/pkg/CFR-2017-title29-vol7/pdf/CFR-2017-title29-vol7-sec1915-1000.pdf. September 7, 2017.

*Page GW. 1981. Comparison of groundwater and surface water for patterns and levels of contamination by toxic substances. Environ Sci Technol 15:1475-1481.

*Pankow JF, Rosen ME. 1988. Determination of volatile compounds in water by purging directly to a capillary column with whole column cryotropping. Environ Sci Technol 22:398-405.

*Parrish CF. 1983. Solvents, industrial. In: Kirk-Othmer encyclopedia of chemical technology. 3rd ed., Vol 21. New York, NY: John Wiley and Sons, 377-401.

Pelkonen O, Vainio H. 1975. Spectral interactions of a series of chlorinated hydrocarbons with cytochrome P-450 of liver microsomes from variously treated rats. Fed Eur Biochem Soc Lett 51:11-14.

*Pellizzari ED. 1982. Analysis for organic vapor emissions near industrial and chemical waste disposal sites. Environ Sci Technol 16:781-785.

*Pellizzari ED, Hartwell TD, Harris BSH, et al. 1982. Purgeable organic compounds in mother's milk. Bull Environ Contam Toxicol 28:322-328.

*Plaa GL, Larson RE. 1965. Relative nephrotoxic properties of chlorinated methane, ethane, and ethylene derivatives in mice. Toxicol Appl Pharmacol 7:37-44.

*Plaa GL, Evans EA, Hine CH. 1958. Relative hepatotoxicity of seven halogenated hydrocarbons. J Pharmacol Exp Ther 123:224-229.

Plaa GL, Traiger GJ, Hanasono GK, et al. 1975. Effect of alcohols on various forms of chemically induced liver injury. Alcohol Liver Pathol [Proc Int Symp Alcohol Drug Res]:225-244.

+*Platt DS, Cockrill BL. 1969. Biochemical changes in rat liver in response to treatment with drugs and other agents. II. Effects of halothane, DDT, other chlorinated hydrocarbons, thioacetamide, dimethylnitrosamine, and ethionine. Biochem Pharmacol 18:445-457.

*Poet TS, Curry TL, Luders TM, et al. 2001. Final report. Pharmacokinetics of 1,1,2-trichloroethane in rats and mice. Submitted to the U.S. Environmental Protection Agency under TSCA. OTS0574377.

*Poet TS, Curry TL, Luders TM, et al. 2003. Amended report. Pharmacokinetics of 1,1,2-trichloroethane in rats and mice. Submitted to the U.S. Environmental Protection Agency under TSCA. EPA HQ-OPPT-200200046.

+*Pozzani UC, Weil CS, Carpenter CP. 1959. The toxicological basis of Threshold Limit Values: 5. The experimental inhalation of vapor mixtures by rats, with notes up on the relationship between single dose inhalation and single dose oral data. Am Ind Hyg Assoc J 20:364-369.

*Rannug U, Sundvall A, Ramel C. 1978. The mutagenic effect of 1,2-dichloroethane on *Salmonella typhimurium* I. Activation through conjugation with glutathione *in vitro*. Chem Biol Interact 20:1-16.

*Riddick JA, Bunger WB, Sakano TK. 1986. Organic solvents: Physical properties and methods of purification. In: Techniques of chemistry, 4th ed. New York, NY: Wiley-Interscience.

*RIDH. 1989. Written communication regarding 1,1,2-trichloroethane levels in private well water. Providence, RI: Rhode Island Department of Health. (May 2).

*Rogers SE, Peterson DL, Lauer WC. 1987. Organic contaminants removal for potable reuse. J Wat Pollut Control Fed 59:722-732.

*Roldan-Arjona T, Garcia-Pedrajas MD, Luque-Romero FL, et al. 1991. An association between mutagenicity of the Ara test of *Salmonella typhimurium* and carcinogenicity in rodents for 16 halogenated aliphatic hydrocarbons. Mutagenesis 6(3):199-205.

8. REFERENCES

*Rooney Al, Boyles AL, Wolfe MS, et al. 2014. Systematic review and evidence integration for literature-based environmental health science assessments. Environ Health Perspect 122:711-718. http://doi.org/10.1289/ehp.1307972.

RTECS. 1988. Registry of Toxic Effects of Chemical Substances. Online: 8/4/88.

*Sabel GV, Clark TP. 1984. Volatile organic compounds as indicators of municipal solid waste leachate contamination. Waste Manag Res 2:119-130.

*Sabljic A. 1987. On the prediction of soil sorption coefficients of organic pollutants from molecular structure: Application of molecular topology model. Environ Sci Technol 21:358-366.

+*Sanders VM, White KL Jr, Shopp GM Jr, et al. 1985. Humoral and cell-mediated immune status of mice exposed to 1,1,2-trichloroethane. Drug Chem Toxicol 8:357-372.

*SANSS. 1988. Structure and Nomenclature Search System. Online. 7/31/88.

*Sapphire Group. 2003. Physiologically based pharmacokinetic model development, simulations, and sensitivity analysis for repeated exposure to 1,1,2-trichloroethane. The Sapphire Group. HAP Task Force. EPA-HQ-OPPT-2002-0046-0007. https://www.regulations.gov/document?D=EPA-HQ-OPPT-2002-0046-0007. March 07, 2018.

*Sapphire Group. 2004a. Route-to-route extrapolation of 1,1,2-trichloroethane studies from the oral route to inhalation using physiologically based pharmacokinetic models: Immunotoxicity. The Sapphire Group. HAP Task Force. EPA-HQ-OPPT-2002-0056-0092. https://www.regulations.gov/document?D=EPA-HQ-OPPT-2002-0056-0092. March 07, 2018.

*Sapphire Group. 2004b. Route-to-route extrapolation of 1,1,2-trichloroethane studies from the oral route to inhalation using physiologically based pharmacokinetic models: Acute neurotoxicity. The Sapphire Group. HAP Task Force. EPA-HQ-OPPT-2002-0056-0130. https://www.regulations.gov/document?D=EPA-HQ-OPPT-2002-0056-0130. March 07, 2018.

*Sapphire Group. 2004c. Route-to-route extrapolation of 1,1,2-trichloroethane studies from the oral route to inhalation using physiologically based pharmacokinetic models: Carcinogenicity. The Sapphire Group. HAP Task Force. EPA-HQ-OPPT-2002-0046-0009. https://www.regulations.gov/document?D=EPA-HQ-OPPT-2002-0046-0009. March 07, 2018.

*Sapphire Group. 2005a. Route-to-route extrapolation of 1,1,2-trichloroethane studies from the oral route to inhalation using physiologically based pharmacokinetic models: Subchronic neurotoxicity. The Sapphire Group. HAP Task Force. EPA-HQ-OPPT-2002-0046-0017. https://www.regulations.gov/document?D=EPA-HQ-OPPT-2002-0046-0017. March 07, 2018.

*Sapphire Group. 2005b. Route-to-route extrapolation of 1,1,2-trichloroethane studies from the oral route to inhalation using physiologically based pharmacokinetic models: Developmental toxicity. The Sapphire Group. HAP Task Force. EPA-HQ-OPPT-2002-0046-0018. https://www.regulations.gov/document?D=EPA-HQ-OPPT-2002-0046-0018. March 07, 2018.

*Sapphire Group. 2006. Route-to-route extrapolation of 1,1,2-trichloroethane studies from the oral route to inhalation using physiologically based pharmacokinetic models: Reproductive toxicity. The Sapphire Group. HAP Task Force. EPA-HQ-OPPT-2002-0056-0128. https://www.regulations.gov/document?D=EPA-HQ-OPPT-2002-0056-0128. March 07, 2018.

SARA (Superfund Amendments and Reauthorization Act). 1986. 99th Congress, Second Session. House of Representatives Report No. 99-962.

*Sato A, Nakajima T. 1979. A structure-activity relationship of some chlorinated hydrocarbons. Arch Environ Health 34:69-75.

Sato A, Nakajima T. 1987. Pharmacokinetics of organic solvent vapors in relation to their toxicity. Scand J Work Environ Health 13:81-93.

*Seidenberg JM, Becker RA. 1987. A summary of the results of 55 chemicals screened for developmental toxicity in mice. Teratogen Carcinogen Mutagen 7:17-28.

+*Seidenberg JM, Anderson DG, Becker RA. 1986. Validation of an *in vivo* developmental toxicity screen in the mouse. Teratogen Carcinogen Mutagen 6:361-374.

*Seip HM, Alstad J, Carlberg GE, et al. 1986. Measurement of mobility of organic compounds in soils. Sci Total Environ 50:87-102.

8. REFERENCES

*Shackelford WM, Cline DM, Faas L, et al. 1983. An evaluation of automated spectrum matching for survey identification of wastewater components by gas chromatography-mass spectroscopy [Supplemental data]. Anal Chem Acta 146:15-27.

*Shah JJ, Heyerdahl EK. 1988. National Ambient Volatile Organic Compounds (VOCs). Data base update. Research Triangle Park, NC: U.S. Environmental Protection Agency, Atmospheric Sciences Research Laboratory. EPA600388010. PB88195631.

*Simmon VF, Kauhanen K, Tardiff RG. 1977. Mutagenic activity of chemicals identified in drinking water. Dev Toxicol Environ Sci 2:249-258.

*Singh HB, Salas LJ, Cavanagh LA. 1977. Distribution sources and sinks of atmospheric halogenated compounds. J Air Pollut Control Assoc 27:332-336.

*Singh HB, Salas LJ, Smith AJ, et al. 1981. Measurements of some potentially hazardous organic chemicals in urban environments. Atmos Environ 15:601-612.

*Singh HB, Salas LJ, Stiles RE. 1982. Distribution of selected gaseous organic mutagens and suspect carcinogens in ambient air. Environ Sci Technol 16:872-880.

*Sipes IG, Gandolfi AJ. 1980. *In vitro* comparative bioactivation of aliphatic halogenated hydrocarbons. Dev Toxicol Environ Sci 8:501-506.

+*Smyth HF, Jr, Carpenter CP, Weil CS, et al. 1969. Range-finding toxicity data: List VII. Am Ind Hyg Assoc J 30:470-476.

*SRI. 1988. Guide to chemical producers. Menlo Park, CA: SRI International.

*Stanley JS. 1986. Broad scan analysis of the FY82 national human adipose tissue survey specimens. Vol 1. Executive Summary. Washington, DC: U.S. Environmental Protection Agency. EPA560586035.

Stewart RD. 1983. Trichloroethanes. In: Encyclopedia of occupational health and safety. Vol 2. National Institutes of Occupational Safety and Health, 2213-2214.

*STORET. 1988. EPA STORET Water Quality Data Base. Online. 10/14/88.

Story DL, Gee SJ, Tyson CA, et al. 1983. Response of isolated hepatocytes to organic and inorganic cytotoxins. J Toxicol Environ Health 11:483-501.

+*Story DL, Meierhenry EF, Tyson CA, et al. 1986. Differences in rat liver enzyme-altered foci produced by chlorinated aliphatics and phenobarbital. Toxicol Ind Health 2:351-362.

*Tabak HH, Quave SA, Mashni CI, et al. 1981. Biodegradability studies with organic priority pollutant compounds. J Water Pollut Control Fed 53:1503-1518.

*Tafazoli M, Kirsch-Volders M. 1996. *In vitro* mutagenicity and genotoxicity study of 1,2dichloroethylene, 1,1,2-trichloroethane, 1,3-dichloropropane, 1,2,3-trichloropropane and 1,1,3trichloropropene, using the micronucleus test and the alkaline single cell gel electrophoresis technique (comet assay) in human lymphocytes. Mutat Res 371(3-4):185-202. http://www.ncbi.nlm.nih.gov/pubmed/9008720.

+*Takahara K. 1986a. [Experimental study on toxicity of trichloroethane: Part 1. Organ distribution of 1,1,1- and 1,1,2-trichloroethanes in exposed mice.] Okayama Igakkai Zasshi 98:1079-1090. (Japanese)

*Takahara K. 1986b. [Experimental study on toxicity of trichloroethane. II. 1,1,1- and 1,1,2-trichloroethane in expired air and in urine of mice. Okayama Igakkai Zasshi 98:1091-1097. (Japanese)

*Takahara K. 1986c. [Experimental study on toxicity of trichloroethane. III. Changes in liver function of mice after exposure to 1,1,1- and 1,1,2-trichloroethane.] Okayama Igakkai Zasshi 98:1099-1109. (Japanese)

Takano T, Miyazaki Y. 1982. Effect of chlorinated ethanes and ethylenes on electron transport in rat liver mitochondria. J Toxicol Sci 7:143-149.

Takano T, Miyazaki Y, Motohashi Y. 1984. Spectral changes of cytochrome P450 and reduction oxidation transition of pyridine nucleotides associated with 1,1,1-trichloroethane and 1,1,2-trichloroethane metabolism in perfused rat liver. 68th Annual Meeting of the Federation of American Societies for Experimental Biology, St Louis, MO. (Abstract) Fed Proc Vol 43.

Takano T, Miyazaki Y, Motohashi Y. 1985. Interaction of trichloroethane isomers with cytochrome P-450 in the perfused rat liver. Fundam Appl Toxicol 5:353-360.

*Taningher M, Parodi S, Grilli S, et al. 1991. Lack of correlation between alkaline DNA fragmentation and DNA covalent binding induced by polychloroethanes after *in vivo* administration. Problems related to the assessment of a carcinogenic hazard. Cancer Detect Prev 15(1):35-39.

*Tham R, Bunnfors I, Eriksson B, et al. 1984. Vestibulo-ocular disturbances in rats exposed to organic solvents. Acta Pharmacol Toxicol 54:58-63.

*Thomas R. 1982. Volatilization from water. In: Lyman WJ, Reehl WF, Rosenblatt DH, eds. Handbook of chemical property estimation methods. New York, NY: McGraw Hill, 15-l to 15-34.

*Thomas R, Byrne M, Gilbert D, et al. 1982. An exposure and risk assessment for trichloroethanes 1,1,1-trichloroethane, 1,1,2-trichloroethane. Washington, DC: U.S. Environmental Protection Agency. EPA440485018.

Thomas R, Byrne M, Gilbert D, et al. 1985. Exposure and risk assessment for trichloroethanes: 1,1,1-Trichloroethane, 1,1,2-trichloroethane. Washington, DC: U.S. Environmental Protection Agency, Office of Water Regulations and Standards. PB85-220598.

Thompson JA, Ho B, Mastovich SL. 1984. Reductive metabolism of 1,1,1,2-tetrachloroethane and related chloroethanes by rat liver microsomes. Chem Biol Interact 51:321-333.

Thompson JA, Ho B, Mastovich SL. 1985. Dynamic headspace analysis of volatile metabolites from the reductive dehalogenation of trichloro- and tetrachloroethanes by hepatic microsomes. Anal Biochem 145:376-384.

Toftgard R, Gustafsson J-A. 1980. Biotransformation of organic solvents: A review. Scand J Work Environ Health 6:1-18.

+*Torkelson TR, Rowe VK. 1981. In: Clayton D, Clayton F, eds. Patty's industrial hygiene and toxicology. 3rd rev ed. New York, NY: John Wiley & Sons, Inc., 3510-3513; 3586-3593.

*Traiger GJ, Plaa GL. 1974. Chlorinated hydrocarbon toxicity: Potentiation by isopropyl alcohol and acetone. Arch Environ Health 28(5):276-278.

*TRI16. 2017. TRI explorer: Providing access to EPA’s toxics release inventory data. Washington, DC: U.S. Environmental Protection Agency, Office of Information Analysis and Access, Office of Environmental Information. Toxics Release Inventory. http://www.epa.gov/triexplorer/. September 27, 2017.

*Tsuruta H. 1975. Percutaneous absorption of organic solvents. 1. Comparative study of the *in vivo* percutaneous absorption of chlorinated solvents in mice. Ind Health 13:227-236.

Tsuruta H. 1986. Percutaneous absorption of chemical substances and toxicity especially about organic solvents. Eisei Kagaku 32:229-241.

*Tsuruta H, Iwasaki K, Fukuda K. 1983. Analysis of trace impurities in reagent and technical grade trichloroethylene. Ind Health 21:293-295.

*Tu AS, Murray TA, Hatch KM, et al. 1985. *In vitro* transformation of BALB/C-3T3 cells by chlorinated ethanes and ethylenes. Cancer Lett 28:85-92.

+*Tyson CA, Hawk-Prather K, Story DL, et al. 1983. Correlations of *in vitro* and *in vivo* hepatotoxicity for five haloalkanes. Toxicol Appl Pharmacol 70:289-302.

Tyson CA, Mitoma C, Kalivoda J. 1980. Evaluation of hepatocytes isolated by a nonperfusion technique in a prescreen for cytotoxicity. J Toxicol Environ Health 6:197-205.

*USDHHS. 1985. U.S. Department of Health and Human Services. Fourth Annual Report on Carcinogens. Summary 1985, 199-200.

Van-Dyke RA, Rikans LE. 1970. Effect of volatile anesthetics on aniline hydroxylase and aminopyrine demethylase. Biochem Pharmacol 19:1501-1502.

*Viar and Company. 1987. Contract Laboratory Program Statistical Data Base. April 13, 1987. output.

*Vogel EW, Nivard MJ. 1993. Performance of 181 chemicals in a Drosophila assay predominantly monitoring interchromosomal mitotic recombination. Mutagenesis 8(1):57-81.

*Vogel TM, Criddle CS, McCarty PL. 1987. Transformations of halogenated aliphatic compounds. Environ Sci Technol 21:722-736.

8. REFERENCES

*Volkel W, Friedewald M, Lederer E, et al. 1998. Biotransformation of perchloroethene: dose-dependent excretion of trichloroacetic acid, dichloroacetic acid, and N-acetyl-S-(trichlorovinyl)-L-cysteine in rats and humans after inhalation. Toxicol Appl Pharmacol 153(1):20-27. http://doi.org/10.1006/taap.1998.8548.

Von Oettingen WF. 1937. The halogenated hydrocarbons: Their toxicity and potential dangers. J Ind Hyg Toxicol 19:349-448.

+*Wahlberg JE. 1976. Percutaneous toxicity of solvents. A comparative investigation in the guinea pig with benzene, toluene and 1,1,2-trichloroethane. Ann Occup Hyg 19:115-119.

+*Wahlberg JE. 1984a. Erythema-inducing effects of solvents following epicutaneous administration to man - studied by laser Doppler flowmetry. Scand J Work Environ Health 10:159-162.

+*Wahlberg JE. 1984b. Edema-inducing effects of solvents following topical administration. Dermatosen Beruf Umwelt 32:91-94.

*Wahlberg JE, Boman A. 1979. Comparative percutaneous toxicity of ten industrial solvents in the guinea pig. Scand J Work Environ Health 5:345-351.

*Wallace LA, Pellizzari E, Hartwell T, et al. 1984. Personal exposure to volatile organic compounds. I. Direct measurements in breathing-zone air, drinking water, food and exhaled breath. Environ Res 35:293-319.

+*Watrous WM, Plaa GL. 1972a. Effect of halogenated hydrocarbons on organic ion accumulation by renal cortical slices of rats and mice. Toxicol Appl Pharmacol 22:528-543.

*Watrous WM, Plaa GL. 1972b. The nephrotoxicity of single and multiple doses of aliphatic chlorinated hydrocarbon solvents in male mice. Toxicol Appl Pharmacol 23:640-649.

*Weisburger EK. 1977. Carcinogenicity studies on halogenated hydrocarbons. Environ Health Perspect 21:7-16.

*Westrick JJ, Mello JW, Thomas RF. 1984. The groundwater supply survey. J Am Water Works Assoc 76:52-59.

+*White KL Jr, Sanders VM, Barnes DW, et al. 1985. Toxicology of 1,1,2-trichloroethane in the mouse. Drug Chem Toxicol 8:333-356.

*WHO. 2010. Guidelines for indoor air quality: Selected pollutants. Geneva, Switzerland: World Health Organization. http://www.euro.who.int/__data/assets/pdf_file/0009/128169/e94535.pdf. April 25, 2012.

*WHO. 2017. Guidelines for drinking-water quality. Fourth edition incorporating the first addendum. Geneva, Switzerland: World Health Organization. http://apps.who.int/iris/bitstream/10665/254637/1/9789241549950-eng.pdf?ua=1. February 28, 2017.

*Wikoff D, Urban JD, Harvey S, et al. 2018. Role of risk of bias in systematic review for chemical risk assessment: A case study in understanding the relationship between congenital heart defects and exposures to trichloroethylene. Int J Toxicol 37(2):125-143. http://doi.org/10.1177/1091581818754330.

*Williams, G. 1983. DNA repair tests of 11 chlorinated hydrocarbon analogs. Final Report EPA contract. EPA/OTS, Document No. 40-8324292. OTS0509403.

+*Wilson DT. 2005. A prenatal developmental toxicity study of 1,1,2-trichloroethane via drinking water in rats. WIL Research Laboratories. HAP Task Force. EPA-HQ-OPPT-2002-0056-0115. https://www.regulations.gov/document?D=EPA-HQ-OPPT-2002-0056-0115. March 07, 2018.

*Wilson JT, Enfield CG, Dunlap WJ, et al. 1981. Transport and fate of selected organic pollutants in a sandy soil. J Environ Qual 10:501-506.

*Wilson JT, McNabb, Balkwill DL, et al. 1983. Enumeration and characterization of bacteria indigenous to a shallow water-table aquifer. Ground Water 21:134-142.

*Windholz M, ed. 1983. The Merck Index. An encyclopedia of chemicals, drugs, and biologicals. Rahway, NJ: Merck and Co., Inc., 1378.

8. REFERENCES

+*Wright WH, Schaffer JM. 1932. Critical anthelmintic tests of chlorinated alkyl hydrocarbons and a correlation between the anthelmintic efficacy, chemical structure and physical properties. Am J Hyg 16:325-426.

+*Xia L, Yu T. 1992. Study of the relationship between the hepatotoxicity and free radical induced by 1,1,2-trichloroethane and 1,1,1-trichloroethane in rat. Biomed Environ Sci 5(4):303-313.

*Yllner S. 1971. Metabolism of 1,1,2-trichloroethane-1,2-^{14}C in the mouse. Acta Pharmacol Toxicol 30:248-256.

Zeiger E. 1987. Carcinogenicity of mutagens: Predictive capability of the Salmonella mutagenesis assay for rodent carcinogenicity. Cancer Res 47:1287-1296.

*Zeiger E, Anderson B, Haworth S, et al. 1988. Salmonella mutagenicity tests: IV. Results from the testing of 300 chemicals. Environ Mol Mutagen 11:1-157.

*Zoeteman BCJ, Harmsen K, Linders JBHJ, et al. 1980. Persistent organic pollutants in river water and ground water of the Netherlands. Chemosphere 9:231-249.

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. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

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

APPENDIX A

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S102-1, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,1,2-Trichloroethane
CAS Numbers: 79-00-5
Date: December 2019
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute
***Provisional MRL*:** 0.03 ppm
Critical Effect: Necrosis of the olfactory epithelium (minimal to mild; nasal level IV)
Reference: Kirkpatrick 2001
Point of Departure: $LOAEL_{HEC}$ of 7.5 ppm
Uncertainty Factor: 270
LSE Graph Key: 6
Species: Rat

MRL Summary: A provisional acute-duration inhalation MRL of 0.03 ppm was derived for 1,1,2-trichloroethane based on necrosis in the olfactory epithelium (nasal level IV) of male and female rats exposed to 58 ppm 1,1,2-trichloroethane for 4 hours (Kirkpatrick 2001). The provisional MRL is based on a $LOAEL_{HEC}$ of 7.5 ppm and a total uncertainty factor of 270 (3 for use of a minimal LOAEL, 3 for extrapolation from animals to humans with dosimetric adjustments,10 for human variability, and 3 for an incomplete database).

Selection of the Critical Effect: In the only acute-duration study that subjected tissues to histopathological examinations (Kirkpatrick 2001), rats exposed to 1,1,2-trichloroethane for 4 hours showed evidence of respiratory tract damage (necrosis of the olfactory epithelium at nasal levels III, IV, and V) at ≥58 ppm. This effect was seen at a lower concentration than hepatocellular necrosis in the same study (≥181 ppm). Several other acute-duration inhalation toxicity studies of 1,1,2-trichloroethane identified liver damage and/or neurological effects. A majority of the studies identified changes in serum blood chemistry related to liver function (at ≥800 ppm) or clinical signs of neurotoxicity (at ≥418 ppm); gross or microscopic pathology examinations were not performed (Bonnet et al. 1980; Carlson 1973; De Ceaurriz et al. 1981; Gehring et al. 1968; Lazarew 1929; Takahara 1986a).

The LOAEL for respiratory effects is lower than the LOAELs for other target systems identified in acute-duration studies (hepatic and neurological effects). NOAEL and LOAEL values for acute-duration inhalation exposure are summarized in Table A-1.

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

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Respiratory effects					
F344 rat	4 hours	ND	58	Necrosis of the olfactory epithelium	Kirkpatrick 2001
F344 rat	4 hours	170 (females) 205 (males)	840 (females) 1,474 (males)	Increased protein content of BALF (females)	Kirkpatrick 2001
Liver effects					
F344 rat	4 hours	58	181	Hepatocellular necrosis	Kirkpatrick 2001
Mouse (NS)	3 hours	ND	800	Increased ALT and liver triglycerides; decreased plasma triglycerides and ATP	Takahara 1986a
Albino rat	2 hours	890	2,080	Increased ALT	Carlson 1973
Swiss-Webster mouse	15 hours	ND	3,750	Increased ALT	Gehring 1968
Neurological effects					
Swiss OF_1 mouse	4 hours	ND	418	CNS depression	De Cearrriz et al. 1981
F344 rat	4 hours	ND	840 (females) 1,474 (males)	Sleepiness; decreased respiration	Kirkpatrick 2001
F344 rat	4 hours	ND	1,527	Sleepiness; decreased respiration	Kirkpatrick 2001
Sprague-Dawley rat	6 hours	ND	1,654	Somnolent	Bonnet et al. 1980
Mouse (NS)	2 hours	1,833	2,749	Lie down on side; loss of reflex control	Lazarew 1929
Swiss-Webster mouse	15 hours	ND	3,750	Anesthesia	Gehring 1968

ALT = alanine aminotransferase; BALF = bronchoalveolar lavage fluid; CNS = central nervous system; LOAEL = lowest-observed-adverse-effect level; ND = not determined; NOAEL = no-observed-adverse-effect level

Selection of the Principal Study: The study of Kirkpatrick (2001) was selected as the principal study for deriving a provisional acute-duration inhalation MRL for 1,1,2-trichloroethane because it identified the lowest reliable LOAEL for respiratory effects in the only study that performed histopathological examinations.

Summary of the Principal Study:

Kirkpatrick DT. 2001. Acute inhalation toxicity (with histopathology) study of 1,1,2-trichloroethane (1,1,2-TCE) in rats. WIL Research Laboratories, Inc. HAP Task Force. EPA-HQ-OPPT-2002-0056-0039. WIL-417001. https://www.regulations.gov/document?D=EPA-HQ-OPPT-2002-0056-0039. March 07, 2018.

F344 rats (5/sex/group) were exposed whole-body to 1,1,2-trichloroethane (purity 99.56%) as a vapor at target concentrations of 0, 50, 200, and 1,500 ppm for 4 hours and sacrificed 24 hours after cessation of exposure. Actual (measured) concentrations were 0, 58, 181, and 1,527 ppm. Animals were monitored for mortality and clinical signs of toxicity. The response to a stimulus (noise) was assessed at (approximately) the midpoint of exposure. One day following exposure, detailed physical examinations were performed and body weights were measured. At necropsy, organ weights (of the adrenals, brain, kidneys, liver, lungs, ovaries, and testes) were recorded. Respiratory tract tissues were examined microscopically in animals from all exposure groups; the liver, kidneys, and stomach were additionally examined in animals in the control and high-exposure groups.

Three females exposed at 1,500 ppm died on the day following exposure; although the cause of death was not specified, necrosis of the liver, kidneys, and/or respiratory tract tissues was observed. There was no mortality in males or in other groups of exposed females. All animals exposed at 1,527 ppm showed sleepiness, decreased respiration, and clear discharge of the eyes immediately following exposure; these signs as well as lethargy, hypothermia, and reddish-brown urine were noted on the day following exposure. The incidence of the absence of a response to a stimulus was increased in rats exposed at 1,527 ppm (but was not strictly exposure-related). Rats exposed at 181 and 1,527 ppm lost weight from study days 0 to 1; within 1 day of exposure, the body weights of rats treated at 1,527 ppm were already significantly lower than controls (by 13%). At scheduled necropsy, pale liver and/or dark areas in the stomach, liver, intestines, and/or urinary bladder were noted at 1,527 ppm. Relative kidney and adrenal gland weights were significantly increased (by 19 and 40%, respectively) in 1,527 ppm males; no significant effects were observed in females (possibly owing to the low number of surviving animals). Histopathological changes were noted primarily in the liver and respiratory tract tissues. Hepatocellular centrilobular necrosis was observed in 0/5 males and 4/5 females (minimal to mild) exposed at 181 ppm and 5/5 males and 2/2 females (moderate to severe) exposed at 1,527 ppm (compared to 0/10 controls). The incidence and severity of necrosis of the olfactory epithelium (nasal levels III, IV, and V) increased in an exposure-related manner. Based on statistical analyses (Fisher's exact test) performed for this analysis, the male and female combined incidence of necrosis was significantly increased at all exposure concentrations at nasal level IV (affecting a small number of cells), and at 181 and 1,527 ppm at nasal levels III and V. The severity of the lesions were graded as minimal (2/5 males and 3/5 females) or mild (2/5 females) at 58 ppm, mild (5/5 males and 5/5 females) at 181 ppm, and mild (3/5 males) or moderate (1/5 males and 2/2 females) at 1,527 ppm. There was no evidence for necrosis of these tissues in control animals.

Selection of the Point of Departure for the provisional MRL: The LOAEL of 58 ppm was selected as the point of departure (POD) for deriving a provisional acute-duration inhalation MRL for 1,1,2-trichloroethane. Incidence data for necrosis of the olfactory epithelium in rats (level IV; any severity) are shown in Table A-2.

Table A-2. Incidence of Necrosis of the Olfactory Epithelium in F344 Rats Exposed to 1,1,2-Trichloroethane for 4 Hours

	Exposure concentration (ppm)			
Target	0	50	200	1,500
Measured	0	58	181	1,527
Necrosis; level IV	0/10 (0%)	7/10 (70%)	10/10 (100%)	7/7 (100%)[a]

[a]Data for three females that died on the day following exposure were excluded from analyses.

Source: Kirkpatrick 2001

These data were not considered amenable to benchmark dose (BMD) modeling because the lowest tested concentration shows a response that is substantially higher than the benchmark response (BMR) of 10% (i.e., 70% of animals were affected at 58 ppm). Thus, the data provide limited information on the dose-response relationship at lower concentrations. In addition, since the response was 100% at the two highest tested exposure concentrations, higher exposure concentrations did not reduce the uncertainty associated with the shape of the dose-response curve.

Human Equivalent Concentration: The LOAEL of 58 ppm was converted to a human equivalent concentration (HEC) of 7.5 ppm using the following equation:

$$LOAEL_{HEC} = LOAEL \times RGDR_{ET}$$

where $RGDR_{ET}$ is the extrathoracic regional gas dose ratio (animal:human) for the extrathoracic region. Extrathoracic regional gas doses were calculated for each species as follows: V_E (minute volume) ÷ SA_{ET} (surface area of the extrathoracic region); where V_E = 137 mL/minute (based on reference body weight for males and females, 0.180 kg) and SA_{ET} = 15 cm^2 in rats and V_E = 13,800 mL/minute and SA_{ET} = 200 cm^2 in humans (EPA 1994).

$$LOAEL_{[HEC]} = LOAEL \times RGDR_{ET}$$
$$LOAEL_{[HEC]} = 58 \text{ ppm} \times (137 \text{ mL/minute} \div 15 \text{ cm}^2)/(13{,}800 \text{ mL/minute} \div 200 \text{ cm}^2)$$
$$LOAEL_{[HEC]} = 58 \text{ ppm} \times 0.13$$
$$LOAEL_{[HEC]} = 7.5 \text{ ppm}$$

Uncertainty Factor: The $LOAEL_{HEC}$ was divided by a total uncertainty factor of 270:

- 3 for extrapolation from a minimal LOAEL; the study authors classified the severity of necrosis as minimal to mild because necrosis affected a small number of cells.
- 3 for extrapolation from animals to humans with dosimetric adjustments
- 10 for human variability
- 3 as a modifying factor for database deficiency because the only acute exposure data are from a single 4-hour exposure study.

$$\text{Provisional MRL} = LOAEL_{HEC} \div UFs$$
$$7.5 \text{ ppm} \div (3 \times 3 \times 10 \times 3) = 0.03 \text{ ppm}$$

Other Additional Studies or Pertinent Information that Lend Support to this Provisional MRL: Histopathological changes to the olfactory epithelium (vacuolization/microcyst formation) were observed following intermediate-duration oral exposure to 1,1,2-trichloroethane (Kirkpatrick 2002).

Agency Contacts (Chemical Manager): Jennifer Przybyla

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,1,2-Trichloroethane
CAS Numbers: 79-00-5
Date: December 2019
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Intermediate
Provisional MRL: 0.002 ppm
Critical Effect: Lesions of the olfactory epithelium (vacuolization/microcyst formation)
Reference: Kirkpatrick 2002
Point of Departure: $BMDL_{10[HEC]}$ of 0.07 ppm
Uncertainty Factor: 30
LSE Graph Key: 13
Species: Rat

MRL Summary: A provisional intermediate-duration inhalation MRL of 0.002 ppm was derived for 1,1,2-trichloroethane based on an increase in the incidence of vacuolization/microcyst formation in the olfactory epithelium of male and female rats exposed to 40 ppm 1,1,2-trichloroethane 6 hours/day, 5 days/week for 13 weeks (Kirkpatrick 2002). The provisional MRL is based on a $BMDL_{10[HEC]}$ of 0.07 ppm and a total uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability).

Selection of the Critical Effect: Only one study evaluated intermediate-duration inhalation toxicity of 1,1,2-trichloroethane (Kirkpatrick 2002). This study identified two targets of toxicity: the respiratory tract and the liver.

Based on a comparison of the lowest LOAEL for these endpoints, the respiratory tract appears to be the most sensitive target of toxicity. At concentrations of 40 and 100 ppm, significantly increased incidences of atrophy and vacuolization/microcyst formation of the olfactory epithelium were observed in male and female rats; the incidence of respiratory epithelial metaplasia of the olfactory epithelium was also significantly increased at 100 ppm (Kirkpatrick 2002). The incidence of these respiratory effects was not significantly increased at 15 ppm relative to controls. A significantly increased incidence of liver effects (namely hepatocellular vacuolization) was seen in the same study at 100 ppm only. Although increased cholesterol was noted in female rats exposed at concentrations as low as 40 ppm, the toxicological significance of this effect is unclear in the absence of effects on other serum chemistry parameters (AST, ALT) and liver weight, and owing to the small magnitude of change in this parameter (within 20% of control values at all concentrations).

Selection of the Principal Study: Kirkpatrick (2002) was selected as the principal study because it was the only study that evaluated the toxicity of 1,1,2-trichloroethane following intermediate-duration exposure.

Summary of the Principal Study:

Kirkpatrick DT. 2002. A 90-day inhalation toxicity study of 1,1,2-trichloroethane (1,1,2-TCE) in rats (with satellite groups for pharmacokinetic evaluations in rats and mice) WIL Research Laboratories, Inc. HAP Task Force. EPA-HQ-OPPT-2002-0046-0003. WIL-417002. https://www.regulations.gov/document?D=EPA-HQ-OPPT-2002-0046-0003.

Fischer 344 CDF Crl:BR rats (10/sex/group) were exposed whole-body to 1,1,2-trichloroethane (purity 99.5%) as a vapor at 0, 15, 40, and 100 ppm 6 hours/day, 5 days/week for 13 weeks. Rats were monitored for mortality and clinical signs of toxicity. Food consumption and body weights were measured weekly. Hematology and clinical chemistry parameters were evaluated at study termination. Ophthalmological examinations were performed. All animals were subjected to necropsy; organ weights (kidneys, liver, lungs, heart, brain, spleen, adrenals, thymus, thyroid, parathyroid, ovaries, testes, and epididymides) were recorded. Comprehensive histopathological examinations were performed on all animals allocated to the high-exposure and control groups; select tissues were examined in all dose groups (e.g., liver, kidneys, and respiratory tissues). Cross-sections of nasal tissues from six nasal levels were prepared using methods described by Morgan (1991).

No significant, exposure-related effects on mortality, clinical signs of toxicity, food consumption, or body weights were reported. There were no significant effects on hematology parameters. Male rats exposed to 100 ppm and female rats exposed to 40 and 100 ppm showed significantly increased levels of serum cholesterol; however, this effect was not strictly dose-related. Serum glucose was significantly decreased in 100 ppm females (but not males). There were no significant effects on other serum chemistry measurements indicative of liver function. Ophthalmological examinations did not reveal significant differences among exposed rats and controls. No significant, exposure-related macroscopic changes were reported. Rats of both sexes treated at 40 and 100 ppm showed lesions of the olfactory epithelium of the nasal turbinates, including atrophy and vacuolization/microcyst formation (accompanied by respiratory epithelial metaplasia at 100 ppm). Also at 100 ppm, hepatocellular vacuolization (minimal in severity) was noted in rats of both sexes. Incidences of vacuolization/microcyst formation and atrophy are presented in Table A-3.

Table A-3. Incidence of Nasal Olfactory Epithelial Lesions in F344 Rats Exposed to 1,1,2-Trichloroethane 6 Hours/Day, 5 Days/Week for 13 Weeks

	Exposure concentration (ppm)			
Nominal	0	15	40	100
Duration adjusted	0	2.7	7.1	17.9
Vacuolization/microcyst formation	2/20 (10%)	6/20 (30%)	10/20 (50%)	18/20 (90%)
Atrophy	0/20 (0%)	0/20 (0%)	13/20 (65%)	17/20 (85%)

Source: Kirkpatrick 2002

Selection of the Point of Departure for the Provisional MRL: The $BMDL_{10[ADJ]}$ of 0.57 ppm for increased incidence vacuolization/microcyst formation of the olfactory epithelium was selected as the basis of the provisional MRL.

BMD modeling was conducted to identify a POD using concentrations adjusted for intermittent exposure and incidence data for vacuolization/microcyst formation and atrophy in the olfactory epithelium. Concentrations of 0, 15, 40, and 100 ppm were adjusted for intermittent exposure (6 hours/24 hours and 5 days/7 days) resulting in adjusted concentrations of 0, 2.7, 7.1, and 17.9 ppm. The data were fit to all available dichotomous models in EPA's Benchmark Software (BMDS version 2.6.0). A BMR of 10% was selected in the absence of data that would support a lower BMR. In accordance with EPA (2012) guidance, BMCs and BMCLs (95% lower confidence limit on the benchmark concentration)associated with an extra risk of 10% are calculated for all models. Adequate model fit is judged by three criteria: goodness-of-fit ($p>0.1$), visual inspection of the dose-response curve, and scaled residual at the data point

(except the control) closest to the predefined BMR. Among all of the models providing adequate fit to the data, the BMCL from the model with the lowest Akaike's Information Criterion (AIC) is selected as the POD when the difference between the BMCLs estimated from these models was >3-fold; otherwise, the BMCL from the model with the lowest AIC was chosen. None of the BMD models provided adequate fit to the atrophy data. Details of the modeling results for vacuolization/microcyst formation are in Table A-4 and Figure A-1.

Table A-4. Model Predictions for Vacuolization/Microcyst Formation of the Olfactory Epithelium in Male and Female Fischer 344 Rats Administered 1,1,2-Trichloroethane via Inhalation for 13 Weeks (Kirkpatrick 2002)

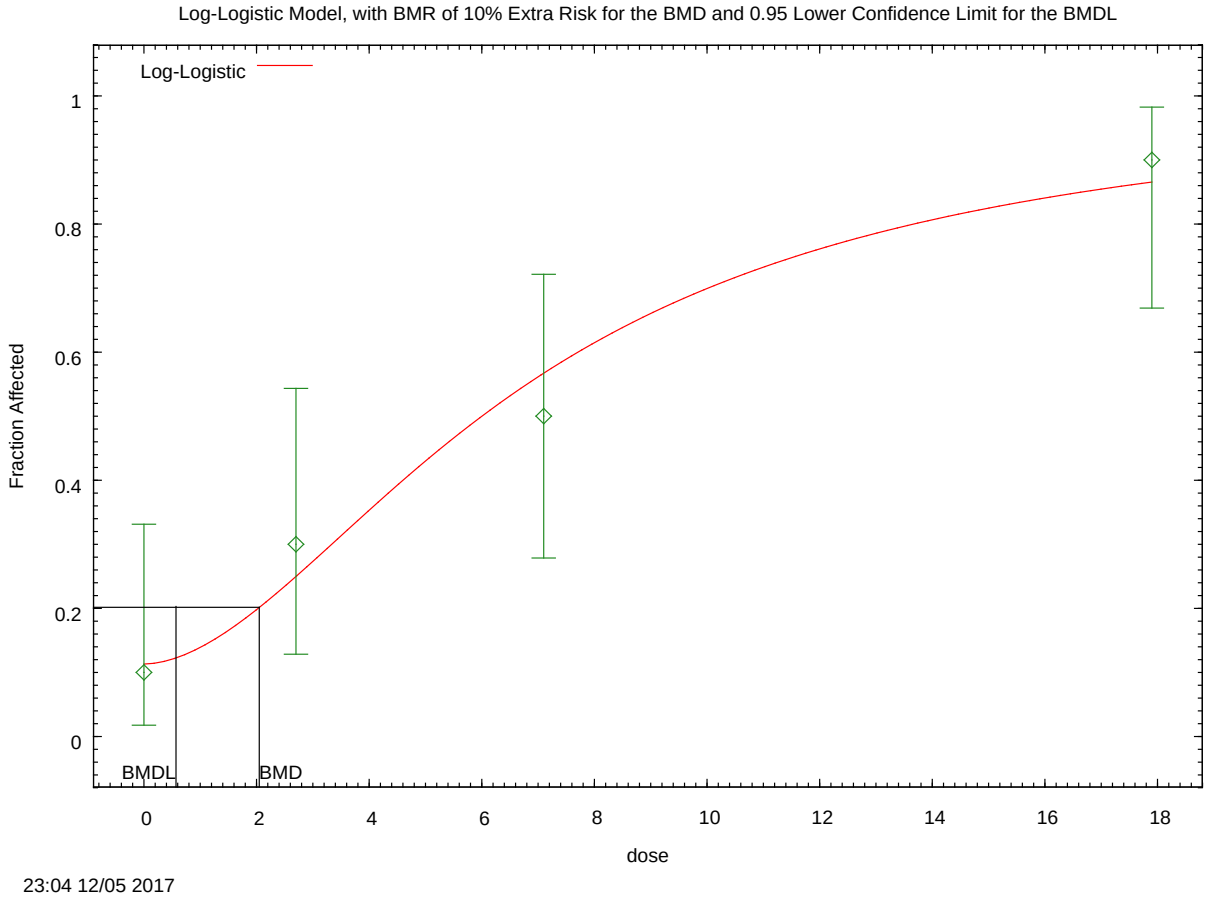
Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b] Dose below BMC	Dose above BMC	Overall largest	AIC	BMC_{10} (ppm)	$BMCL_{10}$ (ppm)
Gamma[c]	1	0.33	0.56	-0.07	0.32	-0.42	84.50	1.64	0.74
Logistic	2	0.79	0.67	-0.67	0.50	-0.67	82.99	2.38	1.76
LogLogistic[d,e]	**1**	**0.88**	**0.35**	**-0.18**	**0.51**	**-0.63**	**85.05**	**2.05**	**0.57**
LogProbit[d]	1	0.86	0.35	-0.13	0.47	-0.67	85.03	2.05	1.29
Multistage (1-degree)[f]	2	0.66	0.72	0.14	-0.12	-0.57	82.86	1.02	0.72
Multistage (2-degree)[f]	1	0.14	0.71	-0.08	0.26	0.26	84.30	1.42	0.75
Multistage (3-degree)[f]	1	0.06	0.80	-0.06	0.20	0.20	84.23	1.31	0.75
Probit	2	0.79	0.68	-0.65	0.48	-0.65	82.99	2.32	1.77
Weibull[c]	1	0.26	0.61	-0.09	0.32	-0.36	84.43	1.61	0.74

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Selected model. All models provided adequate fit to the data. BMCLs for models providing adequate fit were not sufficiently close (differed by >3 fold), so the model with the lowest BMCL was selected (Log logistic).
[f]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom

In accordance with the selection criteria mentioned above, the Log-Logistic model was selected as the POD for vacuolization/microcyst formation. The exposure-response curve is shown in Figure A-1.

Figure A-1. Fit of Log-Logistic Model to Data on 1,1,2-Trichloroethane, Incidence of Vacuolization/Microcyst Formation in Male and Female Rats



Two PODs were considered for the provisional MRL:

- $BMDL_{10[ADJ]}$ of 0.57 ppm based on increased incidence vacuolization/microcyst formation of the olfactory epithelium
- $NOAEL_{[ADJ]}$ of 2.7 ppm based on increased incidence atrophy of the olfactory epithelium (the incidence of this effect was 0% at 15 ppm [adjusted concentration = 2.7 ppm] but was significantly increased relative to controls at 40 ppm [adjusted concentration = 7.1 ppm]).

The $BMDL_{10[ADJ]}$ of 0.57 ppm for increased incidence vacuolization/microcyst formation of the olfactory epithelium was selected as the basis of the provisional MRL since it provided the lowest POD.

Intermittent Exposure: Concentrations of 0, 15, 40, and 100 ppm were adjusted for intermittent exposure (6 hours/24 hours and 5 days/7 days) resulting in adjusted concentrations of 0, 2.7, 7.1, and 17.9 ppm.

Human Equivalent Concentration: The $BMDL_{10[ADJ]}$ of 0.57 ppm was converted to a human equivalent concentration (HEC) of 0.07 ppm using the following equation:

$$BMDL_{HEC} = BMDL_{ADJ} \times RGDR_{ET}$$

where $RGDR_{ET}$ is the extrathoracic regional gas dose ratio (animal:human) for the extrathoracic region. Extrathoracic regional gas doses were calculated for each species as follows: V_E (minute volume) ÷ SA_{ET} (surface area of the extrathoracic region); where V_E = 137 mL/minute (based on reference body weight for males and females, 0.180 kg) and SA_{ET} = 15 cm^2 in rats and V_E = 13,800 mL/minute and SA_{ET} = 200 cm^2 in humans (EPA 1994).

$BMDL_{10[HEC]} = BMDL10_{ADJ}$ x $RGDR_{ET}$
$BMDL_{10[HEC]}$ = 0.57 ppm x (137 mL/minute ÷ 15 cm^2)/(13,800 mL/minute ÷ 200 cm^2)
$BMDL_{10[HEC]}$ = 0.57 ppm x 0.13
$BMDL_{10[HEC]}$ = 0.07 ppm

Uncertainty Factor: The $BMDL_{10[HEC]}$ was divided by a total uncertainty factor of 30:

- 3 for extrapolation from animals to humans with dosimetric adjustments
- 10 for human variability

Provisional MRL = $BMDL_{10[HEC]}$ ÷ UFs
0.07 ppm ÷ (3 x 10) = 0.002 ppm

Other Additional Studies or Pertinent Information that Lend Support to this Provisional MRL: Histopathological changes to the olfactory epithelium (necrosis) were observed following acute-duration oral exposure to 1,1,2-trichloroethane (Kirkpatrick 2001).

Agency Contacts (Chemical Manager): Jennifer Przybyla

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,1,2-Trichloroethane
CAS Numbers: 79-00-5
Date: December 1989
Updated literature search conducted in March 2017
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Chronic

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

Rationale for Not Deriving an MRL: No chronic-duration inhalation studies were identified for 1,1,2-trichloroethane.

Agency Contacts (Chemical Manager): Jennifer Przybyla

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,1,2-Trichloroethane
CAS Numbers: 79-00-5
Date: December 2019
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute
Provisional MRL: 0.5 mg/kg/day
Critical Effect: Increased liver enzymes (AST and ALT)
Reference: Tyson et al. 1983
Point of Departure: NOAEL of 46 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 3
Species: Rat

MRL Summary: A provisional acute-duration oral MRL of 0.5 mg/kg/day was derived for 1,1,2-trichloroethane based on increased liver enzymes (AST and ALT) in male rats administered 1,1,2-trichloroethane via gavage at doses of approximately 0, 46, 92, or 228 mg/kg/day (Tyson et al. 1983). The provisional MRL is based on a NOAEL of 46 mg/kg and a total uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability).

Selection of the Critical Effect: In an acute toxicity study of male Sprague-Dawley rats administered a single gavage dose of 1,1,2-trichloroethane, a substantial elevation in liver enzymes (AST and ALT) was observed 48 hours after administration of approximately 92 mg/kg; these liver enzymes were not significantly different from controls at 46 mg/kg/day (Tyson et al. 1983; Table A-5). The increase in liver enzymes was observed at a lower dose than effects on liver histopathology (i.e., congestion, fatty degeneration, and edema) in dogs treated at 433 mg/kg/day (Wright and Schaffer 1932), or increased enzymatic activity (of ALT, sorbital dehydrogenase [SDH], and glutamate dehydrogenase) in Wistar rats treated at 667 mg/kg/day (Xia and Yu 1992).

Table A-5. Effects on Liver Enzymes in Male Sprague-Dawley Rats Exposed to 1,1,2-Trichloroethane as a Single Gavage Dose[a]

	Dose (mg/kg)			
Effect	0	46	92	228
ALT (U/L); 24 hours	45±10[b]	29	60	1811[c]
ALT (U/L); 48 hours		38	323	3975[c]
AST (U/L); 24 hours	83±21[b]	72	163	4428[c]
AST (U/L); 48 hours		77	1248[c]	8781[c]

[a]Data for administered doses and enzyme levels were obtained from Figure 9 of the study using GrabIt! Software.
[b]Mean±standard deviation at 6, 24, and 48 hours (as reported in the text of the study).
[c]Measured values as reported in Figure 9 of the study.

Source: Tyson et al. 1983

NOAEL and LOAEL values for acute-duration oral exposure are summarized in Table A-6. The LOAEL for increased liver enzymes is lower than LOAELs identified for other acute effects. Gait impairment and decreased body weight gain (males) were observed at 200 mg/kg in a well-conducted acute neurotoxicity

study (Beck 2004). Although motor activity was reported to be significantly decreased in males at 55 mg/kg in this study (Beck 2004), this effect was transient (observed during only a small window of time, without significant effects on mean total or ambulatory counts), showed high variability, and was not consistent across sexes (motor activity counts were increased, nonsignificantly, in females during the same time period). Several other acute toxicity studies of mice and dogs with 1,1,2-trichloroethane also reported neurological effects at doses higher than that eliciting liver effects in the Tyson et al. (1983) study. Results included sedation in male mice at ≥450 mg/kg/day (White et al. 1985), taste aversion in male mice at ≥100 mg/kg/day (toxicological significance uncertain; Kallman et al. 1983), motor impairment in mice at 128 mg/kg/day (Borzelleca 1983), and drowsiness in dogs at ≥289 mg/kg/day (Wright and Schaffer 1932). LOAELs for effects on other target systems identified in acute-duration toxicity studies (effects on body weight and the gastrointestinal and renal systems) were higher than the LOAEL for increased liver enzymes in male rats.

Selection of the Principal Study: The Tyson et al. (1983) study was selected as the principal study for deriving a provisional acute-duration oral MRL for 1,1,2-trichloroethane because it identified the lowest reliable LOAEL for acute effects.

Summary of the Principal Study:

Tyson CA, Hawk-Prather K, Story DL, et al. 1983. Correlations of *in vitro* and *in vivo* hepatotoxicity for five haloalkanes. Toxicol Appl Pharmacol 70:289-302.

In an acute toxicity study, male Sprague-Dawley rats (number per group not specified) were administered 1,1,2-trichloroethane as a single dose via gavage. Data were presented graphically in Figure 9 of the study report. Doses were estimated using GrabIt! Software; doses were approximately 0, 0.34, 0.69, and 1.71 mmol/kg, or 0, 46, 92, and 228 mg/kg (based on molecular weight of 133.4 g/mol for 1,1,2-trichloroethane). The enzymatic activities of ALT and AST were evaluated 6, 24, and/or 48 hours after dosing. No other evaluations of hepatic toxicity were reported.

Enzyme levels (mean±standard deviation) for the control group were reported in the text of the study. ALT and AST in untreated controls were 45±10 and 83±21 U/L, respectively at 6, 24, and 48 hours post-exposure; the number of animals evaluated at each of these time points was 3, 5 and 5, respectively. Based on data from Figure 9 of the study report (obtained via GrabIt! Software or embedded in the figure), 48 hours after treatment at 92 and 228 mg/kg, ALT and AST activities were increased by approximately 7.2- and 15-fold, respectively, compared to controls (statistical analyses were not performed). In the 46 mg/kg group, there was no significant change in liver enzymes.

Selection of the Point of Departure for the Provisional MRL: The NOAEL of 46 mg/kg/day was selected as the POD for deriving a provisional acute duration oral MRL for 1,1,2-trichloroethane. BMD modeling could not be conducted because information required to perform modeling (e.g., animal numbers, measures of variance) was not reported.

Table A-6. Summary of Relevant NOAEL and LOAEL Values Following Acute-Duration Oral Exposure to 1,1,2-Trichloroethane

Species	Duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Neurological effects					
Crl:CD(SD) IGS rat	Once	95	200	Gait impairment on study day 0 (4/14 males; 5/12 females; 0/12 controls)	Beck 2004
CD-1 mouse	Once	30	100	Taste aversion	Kallman et al. 1983
CD-1 mouse	Once	ND	128	Motor impairment	Borzelleca 1983
Dog (NS)	Once	144	289	Drowsiness	Wright and Schaffer 1932
CD-1 mouse	Once	ND	450	Sedation	White et al. 1985
Liver effects					
Sprague-Dawley rat	Once	46	92	Increased AST and ALT	Tyson et al. 1983
Dog (NS)	Once	144	433	Mild congestion, fatty degeneration and edema	Wright and Schaffer 1932
Wistar rat	Once	ND	667	Increased ALT, SDH, glutamate dehydrogenase	Xia and Yu 1992
Other effects					
Dog (NS)	Once	ND	144	Mild congestion and cloudy swelling of the kidneys	Wright and Schaffer 1932
Wistar-derived Alderley Park rat	7 days	ND	180	Decreased body weight gain	Platt and Cockrill 1969
Crl:CD(SD) IGS rat	Once	95	200	Decreased body weight gain in males	Beck 2004
Dog (NS)	Once	144	433	Mild congestion and inflammation of the gastrointestinal tract	Wright and Schaffer 1932

ALT = alanine aminotransferase; AST = aspartate aminotransferase; LOAEL = lowest-observed-adverse-effect level; ND = not determined; NOAEL = no-observed-adverse-effect level; NS = not specified; SDH = sorbitol dehydrogenase

Uncertainty Factor: The NOAEL of 46 mg/kg/day was divided by a total uncertainty factor of 100:

- 10 for animal to human extrapolation
- 10 for human variability

Provisional MRL = NOAEL ÷ UFs
46 mg/kg ÷ (10 x 10) ≈ 0.5 mg/kg/day

Other Additional Studies or Pertinent Information that Lend Support to this Provisional MRL: In male mice administered 1,1,2-trichloroethane via a single intraperitoneal injection, the reported ED_{50} values for increased serum ALT were approximately 144 mg/kg (based on the ED_{50} reported in mL/kg) and 240 mg/kg (based on the ED_{50} reported in mmol/kg) (Klaassen and Plaa 1966). In an intermediate-duration study, decreased glutathione (males) and changes in microsomal activities (females) were noted in mice administered 1,1,2-trichloroethane at 46 (males) or 44 (females) mg/kg/day in drinking water for 90 days (White et al. 1985). No non-neoplastic liver lesions (based on histopathological examinations) were observed in rats treated at up to 92 mg/kg/day or mice treated at up to 390 mg/kg/day via gavage for 78 weeks (NCI 1978).

Agency Contacts (Chemical Manager): Jennifer Przybyla

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,1,2-Trichloroethane
CAS Numbers: 79-00-5
Date: December 1989
Updated literature search conducted in March 2017
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate
MRL: 0.04 mg/kg/day
Critical Effect: Immunotoxicity (Decreased hemagglutination titers) and mild hepatotoxicity
Reference: Sanders et al. 1985
Point of Departure: NOAEL of 3.9 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 18, 19
Species: Mouse

MRL Summary: An intermediate-duration oral MRL of 0.04 mg/kg/day was derived for 1,1,2-trichloroethane based on immunological and hepatic effects observed in male and female mice exposed to 44 mg/kg/day 1,1,2-trichloroethane in drinking water for 90 days (Sanders et al. 1985; White et al. 1985). The MRL is based on a NOAEL of 3.9 mg/kg/day and a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Selection of the Critical Co-Effects: In two intermediate-duration oral toxicity studies, male and female mice administered 1,1,2-trichloroethane in the drinking water for 90 days showed dose-related effects on the liver (decreased glutathione in males and changes in microsomal activity in females) and the humoral immune system (a reduction in hemagglutination titers) at ≥44 mg/kg/day (Sanders et al. 1985; White et al. 1985). The NOAEL was 3.9 mg/kg/day (females) and 4.4 mg/kg/day (males) based on reduced hemagglutination titers, supported by changes in microsomal activity in females. Increased ALT and absolute and relative liver weights were also observed in females treated at 384 mg/kg/day (White et al. 1985). With respect to immune effects, the ability of thioglycolate-recruited peritoneal exudate cells (PECs) to phagocytize sRBCs was significantly reduced in males treated at 305 mg/kg/day. Cell-mediated immunity was unaffected in both sexes. Hepatic and immune effects were observed at a lower dose than effects on body weight (≥69 mg/kg/day) (Mylchreest 2006; Story et al. 1986; White et al. 1985; Wilson 2005) and development (82.2 mg/kg/day; Mylchreest 2006). No other intermediate-duration oral toxicity studies evaluated immune function. NOAEL and LOAEL values for intermediate-duration oral exposure are summarized in Table A-7.

Table A-7. Summary of Relevant NOAEL and LOAEL Values Following Intermediate-Duration Oral Exposure to 1,1,2-Trichloroethane

Species	Duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
CD-1 mouse	90 days	3.9 F 4.4 M	44 F 46 M	Decreased hemagglutination titers	Sanders et al. 1985
CD-1 mouse	90 days	3.9	44	Decreased glutathione in males; changes in microsomal activity in females	White et al. 1985
		46	305	Decreased body weight in males	
Osborne-Mendel rat	5 days/week, 7 weeks	ND	69	Decreased body weight	Story et al. 1986
Crl:CD(SD) IGS rat	Two generations	40.6	82.2	Decreased body weight gain during gestation (P1 and F1 females)	Mylchreest 2006
				Decreased F1 and F2 pup weights (PNDs 4–21)	
Crl:CD(SD) IGS rat	GDs 6–20	48	111	Decreased body weight gain	Wilson 2005

F = female; GD = gestation day; LOAEL = lowest-observed-adverse-effect level; M = male; ND = not determined; NOAEL = no-observed-adverse-effect level; PND = postnatal day

Selection of the Principal Study: The studies of Sanders et al. (1985) and White et al. (1985) were selected as the principal studies for deriving an intermediate-duration oral MRL for 1,1,2-trichloroethane because they identified a NOAEL (3.9 mg/kg/day) associated with the lowest LOAEL (44 mg/kg/day); the liver and the immune system are sensitive targets of 1,1,2-trichloroethane toxicity. The studies by Sanders et al. (1985) and White et al. (1985) evaluated a comprehensive set of endpoints.

Summary of the Principal Study:

Sanders VM, White KL, Shopp Jr GM, et al. 1985. Humoral and cell-mediated immune status of mice exposed to 1,1,2-trichloroethane. Drug Chem Toxicol 8(5):357-372.

White KL, Sanders VM, Barnes DW, et al. 1985. Toxicology of 1,1,2-trichloroethane in the mouse. Drug Chem Toxicol 8(5):333-355.

In two companion studies, CD-1 mice were administered 1,1,2-trichloroethane (purity 95%) at 0, 20, 200, and 2,000 ppm in the drinking water (equivalent to time-weighted average doses of 0, 4.4, 46, and 305 mg/kg/day for males and 0, 3.9, 44, and 384 mg/kg/day for females based on measured fluid intake and body weight data) for 90 days. Fluid intake, body weights, hematology and clinical chemistry parameters, hepatic microsomal activities, organ weights (brain, liver, spleen, lungs, thymus, kidneys, and testes), and gross (but not microscopic) pathology were evaluated in 32–48 mice/sex/group by White et al. (1985). The study by Sanders et al. (1985) evaluated immunological endpoints in 8–25 mice/sex/group. Humoral immune status was assessed by measuring the numbers of splenic AFCs to sRBCs (on peak day 4 and on day 5), hemagglutination titers, and the response of splenic lymphocytes to lipopolysaccharide (LPS; a B-cell mitogen) and concanavalin A (con A; a T-cell mitogen). Cell-mediated immune function parameters included delayed-type hypersensitivity (DTH) and popliteal lymph node responses to sRBCs. Additional immunological endpoints evaluated were the ability of macrophages of the reticuloendothelial system (RES) to clear sRBC from the vascular system and distribute them to the liver, spleen, thymus, lungs, and kidneys; numbers of PECs (recruitable, adherent, chemotaxis) and their ability to phagocytize sRBCs, and DNA synthesis in the bone marrow.

According to White et al. (1985), male mice treated at 305 mg/kg/day exhibited a significant ($p<0.05$) reduction in fluid intake (more than 30% lower than controls) over the 90-day treatment period; no significant effects on fluid intake were observed in female mice. Exposure to 1,1,2-trichloroethane at 305 mg/kg/day produced a dose-related reduction in body weight gain in male mice; after treatment at this dose for 90 days, body weights were 10% lower than controls. Body weight/body weight gain in female mice was not affected by treatment. In males, liver glutathione was decreased following exposure to ≥46 mg/kg/day (16–28% lower than controls). Females treated at ≥44 mg/kg/day showed minimal effects on microsomal activity (decreased cytochrome P-450 levels and decreased aniline hydroxylase activity). At 384 mg/kg/day, liver glutathione, ALT levels, and absolute and relative liver weights were significantly increased in females. Sanders et al. (1985) reported no significant effects on the humoral immune response based on AFC counts or the response of splenic lymphocytes to B-cell and T-cell mitogens. However, hemagglutination titers (expressed as $\log_2$ titers) were significantly decreased in male and female mice treated at ≥44 mg/kg/day relative to controls. Based on the transformation of $\log_2$ titers to antibody dilutions, hemagglutination levels were decreased 47 and 59% in males treated at 46 and 305 mg/kg/day, respectively, and 40 and 45% in females treated at 44 and 384 mg/kg/day, respectively. Cell-mediated immune responses were unaffected by treatment. Changes in the activity of fixed macrophages of the RES to clear and distribute sRBCs (observed in females only) were not considered treatment-related owing to variations in the direction and magnitude of effects. In male mice treated at 305 mg/kg/day, PECs showed a reduced ability to phagocytize sRBCs (55–56% lower than controls over a 20–45-minute period). No significant time- or dose-related effects on bone marrow DNA synthesis were observed. White et al. (1985) reported no other significant, treatment-related effects on organ

weights (changes in absolute and/or relative organ weights in males were attributed to decreased body weights) or gross pathology.

Selection of the Point of Departure for the MRL: The NOAEL of 3.9 mg/kg/day was selected as the POD for deriving an intermediate-duration oral MRL for 1,1,2-trichloroethane. These data were not amenable to BMD modeling because information required to perform modeling (e.g., animal numbers) was not reported.

Uncertainty Factor: The NOAEL of 3.9 mg/kg/day was divided by a total uncertainty factor of 100:

- 10 for animal to human extrapolation
- 10 for human variability

MRL = NOAEL ÷ UFs
3.9 mg/kg/day ÷ 100 = 0.04 mg/kg/day

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Data from acute-duration oral studies identify the liver as a sensitive target of 1,1,2-trichloroethane-induced toxicity. Liver effects (increased AST, ALT, SDH, and glutamate dehydrogenase, and mild congestion, fatty generation, and edema) were observed in animals treated a single time with 1,1,2-trichloroethane at 60–667 mg/kg (Tyson et al. 1983; Wright and Schaffer 1932; Xia and Yu 1992). Although an acute-duration study in mice exposed to 1,1,2-trichloroethane in drinking water at up to 38 mg/kg/day for 14 days did not identify any significant treatment-related effects on humoral or cell-mediated immunity, this study used lower doses than those used in the intermediate-duration study and did not evaluate a comprehensive set of immunological parameters (Sanders et al. 1985). The available chronic-duration studies did not identify histopathological changes to the liver, spleen, lymph nodes, bone marrow, or thymus of rats (treated at up to 92 mg/kg/day for 78 weeks) or mice (treated at up to 390 mg/kg/day for 78 weeks); however, immune system function was not evaluated (NCI 1978).

Agency Contacts (Chemical Managers): Jennifer Przybyla

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,1,2-Trichloroethane
CAS Numbers: 79-00-5
Date: December 1989
Updated literature search conducted in March 2017
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

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

Rationale for Not Deriving an MRL: No chronic-duration oral MRL was derived for 1,1,2-trichloroethane because the available data are insufficient for identifying a critical effect. No adverse effects were identified in rats administered 1,1,2-trichloroethane via gavage at up to 92 mg/kg/day 5 days/week for 78 weeks (NCI 1978). The only adverse effect seen in mice administered 1,1,2-trichloroethane via gavage at up to 390 mg/kg/day 5 days/week for 78 weeks was increased mortality (at 195 mg/kg/day) and an increase in hepatocellular carcinomas at ≥195 mg/kg/day and adrenal pheochromocytomas at 390 mg/kg/day (NCI 1978).

Agency Contacts (Chemical Manager): Jennifer Przybyla

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR 1,1,2-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 1,1,2-trichloroethane.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen was conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, and chemical interactions for 1,1,2-trichloroethane. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of 1,1,2-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 1,1,2-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
  - Neurological effects
  - Reproductive effects
  - Developmental effects

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

	Other noncancer effects
	Cancer
Toxicokinetics	
	Absorption
	Distribution
	Metabolism
	Excretion
	PBPK models
Biomarkers	
	Biomarkers of exposure
	Biomarkers of effect
Interactions with other chemicals	

B.1.1 Literature Search

The current literature search was intended to update the 1989 toxicological profile for 1,1,2-trichloroethane, thus, the literature search was restricted to studies published between January 1987 and March 2017. The following main databases were searched in March 2017:

- PubMed
- National Library of Medicine's TOXLINE
- 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 1,1,2-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 1,1,2-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	
03/2017	((79-00-5[rn] OR 28E9ERN9WU[rn] OR "1,1,2-trichloroethane"[supplementary concept] OR "1,1,2-trichloroethane"[nm]) AND (1987/01/01 : 3000[dp] OR 1987/01/01 : 3000[mhda])) OR (("1,1,2-Trichlorethane"[tw] OR "1,1,2-Trichloroethane"[tw] OR "1,2,2-Trichloroethane"[tw] OR "beta-Trichloroethane"[tw] OR "Trojchloroetan(1,1,2)"[tw] OR "Vinyl trichloride"[tw] OR "Vinyltrichloride"[tw]) AND (1987/01/01 : 3000[dp] OR 1987/01/01 : 3000[crdat] OR 1987/01/01 : 3000[edat]))
Toxline	
03/2017	("1 1 2-trichlorethane" OR "1 1 2-trichloroethane" OR "1 2 2-trichloroethane" OR "beta-trichloroethane" OR "trojchloroetan (1 1 2) " OR "vinyl trichloride" OR "vinyltrichloride" OR 79-005- [rn]) AND 1987:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
Toxcenter	
03/2017	FILE 'TOXCENTER' ENTERED AT 15:02:54 ON 24 MAR 2017 L1 2396 SEA 79-00-5 L2 2288 SEA L1 NOT TSCATS/FS L3 2135 SEA L2 NOT PATENT/DT L4 1658 SEA L3 AND PY>=1987 ACTIVATE TOXQUERY/Q --------- L5 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L6 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L7 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L8 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L9 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L10 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L11 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L12 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L13 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L14 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L15 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L16 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L17 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)

Table B-2. Database Query Strings

Database search date	Query string
	L18 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L19 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L20 QUE (ENDOCRIN? AND DISRUPT?)
	L21 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L22 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L23 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L24 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L25 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L26 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L27 QUE (NEPHROTOX? OR HEPATOTOX?)
	L28 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L29 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L30 QUE L5 OR L6 OR 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
	L31 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?)
	L32 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L33 QUE L30 OR L31 OR L32
	L34 QUE (NONHUMAN MAMMALS)/ORGN
	L35 QUE L33 OR L34
	L36 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?)
	L37 QUE L35 OR L36

	L38 742 SEA L4 AND L37
	L39 12 SEA L38 AND MEDLINE/FS
	L40 83 SEA L38 AND BIOSIS/FS
	L41 610 SEA L38 AND CAPLUS/FS
	L42 37 SEA L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)
	L43 709 DUP REM L39 L40 L42 L41 (33 DUPLICATES REMOVED)
	L*** DEL 12 S L38 AND MEDLINE/FS
	L*** DEL 12 S L38 AND MEDLINE/FS
	L44 12 SEA L43
	L*** DEL 83 S L38 AND BIOSIS/FS
	L*** DEL 83 S L38 AND BIOSIS/FS

Table B-2. Database Query Strings

Database search date	Query string
	L45 81 SEA L43 L*** DEL 610 S L38 AND CAPLUS/FS L*** DEL 610 S L38 AND CAPLUS/FS L46 584 SEA L43 L*** DEL 37 S L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L*** DEL 37 S L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L47 32 SEA L43 L48 697 SEA (L44 OR L45 OR L46 OR L47) NOT MEDLINE/FS L49 81 SEA L48 AND BIOSIS/FS L50 19 SEA L49 AND PY>1998 L51 113 SEA L48 NOT CAPLUS/FS D SCAN L51 L52 584 SEA L48 AND CAPLUS/FS D SCAN L52

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS[a]	
03/2017	Compound searched: 79-00-5
NTP	
03/2017	79-00-5 1,1,2-Trichlorethane 1,1,2-Trichloroethane 1,2,2-Trichloroethane beta-Trichloroethane Vinyl trichloride Vinyltrichloride
NIH RePORTER	
06/2017	Text Search: "1,1,2-Trichlorethane" OR "1,1,2-Trichloroethane" OR "1,2,2-Trichloroethane" OR "beta-Trichloroethane" OR "Trojchloroetan(1,1,2)" OR "Vinyl trichloride" OR "Vinyltrichloride" (Advanced), Search in: Projects Admin IC: All, Fiscal Year: Active Projects
Other	Identified throughout the assessment process

[a]Several versions of the TSCATS database were searched, as needed, by CASRN including TSCATS1 via Toxline (no date limit), TSCATS2 via https://yosemite.epa.gov/oppts/epatscat8.nsf/ReportSearch?OpenForm (date restricted by EPA receipt date), and TSCATS via CDAT (date restricted by 'Mail Received Date Range'), as well as google for recent TSCA submissions.

The 2017 results were:

- Number of records identified from PubMed, TOXLINE, and TOXCENTER (after duplicate removal): 821
- Number of records identified from other strategies: 77
- Total number of records to undergo literature screening: 898

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on 1,1,2-trichloroethane:

- 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.

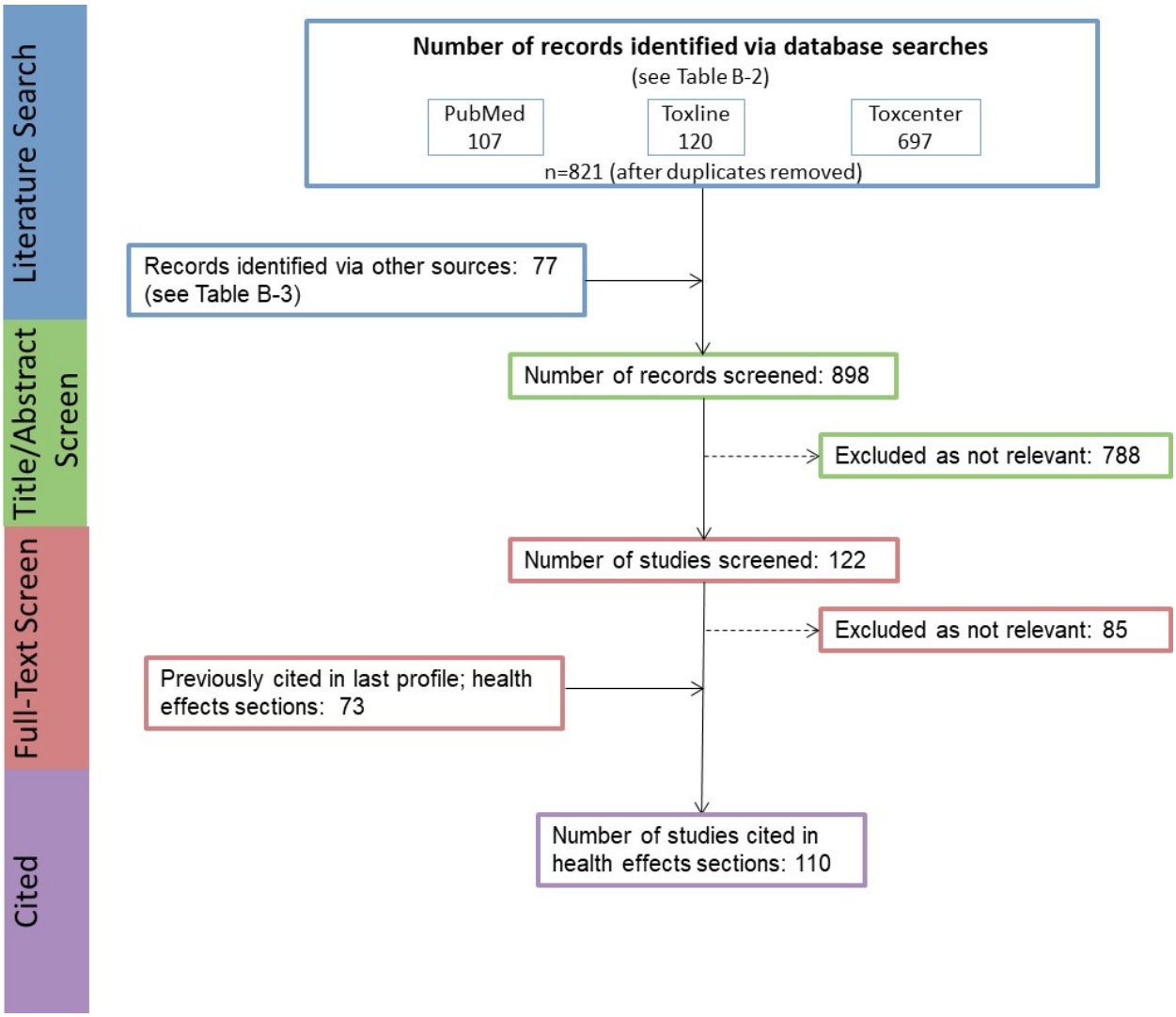
- Number of titles and abstracts screened: 898
- Number of studies considered relevant and moved to the next step: 122

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: 122
- Number of studies cited in the health effects sections of the 1989 toxicological profile: 73
- Total number of studies cited in the health effects sections of the updated profile: 110
- Number of new health effect studies cited in the updated profile: 37

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

Figure B-1. March 2017 Literature Search Results and Screen for 1,1,2-Trichloroethane



APPENDIX C. FRAMEWORK FOR ATSDR'S SYSTEMATIC REVIEW OF HEALTH EFFECTS DATA FOR 1,1,2-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 1,1,2-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 1,1,2-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 1,1,2-trichloroethane. The inclusion criteria used to identify relevant studies examining the health effects of 1,1,2-trichloroethane are presented in Table C-1.

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
Cardiovascular effects
Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects

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

Dermal effects
Ocular effects
Endocrine effects
Immunological effects
Neurological effects
Reproductive effects
Developmental effects
Other noncancer effects
Cancer

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.

C.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

A literature search and screen was conducted to identify studies examining the health effects of 1,1,2-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 literature search to was intended to update the 1989 toxicological profile for 1,1,2-trichloroethane; thus, the literature search was restricted to studies published between 1987 and 2017. See Appendix B for the databases searched and the search strategy.

A total of 821 records relevant to all updated sections of the toxicological profile were identified via database searches (after duplicate removal). An additional 77 records were identified via other sources.

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 1,1,2-trichloroethane.

Title and Abstract Screen. In the Title and Abstract Screen step, 898 records were reviewed; 56 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 the 56 health effects documents identified in the update literature was performed. Additionally, 18 documents cited in the LSE tables for the existing profile were included in the full study screen bringing the total number of documents for the qualitative review to 74. Of the 74 documents undergoing Full Text Screen, 43 documents did not meet the inclusion criteria; some of the excluded studies were used as background information on toxicokinetics or mechanisms of action or were relevant

to other sections of the toxicological profile. The 31 documents selected for inclusion contained 38 unique studies.

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.

A summary of the extracted data for each study is presented in the Supplemental Document for 1,1,2-trichloroethane and overviews of the results of the inhalation, oral, and dermal exposure studies are presented in Sections 2.2–2.19 of the profile and in the Levels Significant Exposures tables (Tables 2-1, 2-2, and 2-3, respectively).

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

C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

Overviews of the potential health effect outcomes for 1,1,2-trichloroethane identified in human and animal studies are presented in Tables C-3 and C-4, respectively. The only available human studies evaluating noncancer effects are dermal studies (limited in scope) and one case-control study examining the association between the proximity to industrial air releases of chlorinated solvents (including 1,1,2-tricholoroethane) and birth defects (Brender et al. 2014). Animal studies examined a comprehensive set of endpoints following inhalation or oral exposure, but dermal studies were limited to acute lethality, skin irritation, and skin sensitization. Respiratory, hepatic, neurological, and

APPENDIX C

Table C-3. Overview of the Health Outcomes for 1,1,2-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	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Case control	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
Population	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Case series	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Oral studies																	
Cohort	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Case control	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Population	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Case series	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Dermal studies																	
Cohort	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Case control	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Population	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Case series	0	0	0	0	0	0	0	0	3	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0

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 1,1,2-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	0	2	0	0	0	0	4	0	0	0	0	0	6	0	0	0	0
	0	2	0	0	0	0	4	0	0	0	0	0	6	0	0	0	0
Intermediate-duration	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0
	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Chronic-duration	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Oral studies																	
Acute-duration	3	1	0	2	1	0	5	2	0	0	0	1	6	1	1	0	0
	2	0	0	2	0	0	3	1	0	0	0	0	5	0	0	0	0
Intermediate-duration	5	1	0	0	1	0	1	1	0	0	0	1	1	1	2	0	0
	4	0	0	0	0	0	1	0	0	0	0	1	0	0	1	0	0
Chronic-duration	2	2	2	2	2	2	2	2	2	0	0	2	2	2	0	0	2
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Dermal studies																	
Acute-duration	0	0	0	0	0	0	0	1	4	0	0	0	1	0	0	0	0
	0	0	0	0	0	0	0	0	3	0	0	0	0	0	0	0	0
Intermediate-duration	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Chronic-duration	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

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.

immunological effects were considered sensitive outcomes, i.e., effects were observed at low concentrations or doses. Thirty-eight studies (published in 31 documents) examining these potential outcomes were carried through to Steps 4–8 of the systematic review.

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?

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

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 1,1,2-trichloroethane health effects studies observed in animal experimental studies (human studies did not evaluate respiratory, hepatic, neurological or immunological outcomes) are presented in Table C-8.

Table C-8. Summary of Risk of Bias Assessment for 1,1,2-Trichloroethane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	Risk of bias tier
Outcome: Respiratory effects									
Inhalation acute exposure									
Kirkpatrick 2001 (rat; F344; 58–1,527 ppm)	++	+	++	++	++	++	++	++	First
Kirkpatrick 2001 (rat; F344; 45–1,474 ppm)	++	+	++	++	++	++	++	++	First
Oral acute exposure									
White et al. 1985 (mouse; CD-1; 14 days)	+	+	++	+	++	+	++	++	First
Inhalation intermediate exposure									
Kirkpatrick 2002 (rat; F344 CDF Crl:BR)	++	++	++	++	++	++	++	++	First
Oral intermediate exposure									
White et al. 1985 (mouse; CD-1)	+	+	++	+	++	+	–	++	Second
Oral chronic exposure									
NCI 1978 (rat; Osborne-Mendel)	+	+	++	+	+	++	++	++	First
NCI 1978 (mouse; B6C3F1)	+	+	++	+	+	++	++	++	First
Outcome: Hepatic effects									
Inhalation acute exposure									
Carlson 1973 (rat; albino)	–	+	+	+	+	–	–	+	Second
Gehring 1968 (mouse; Swiss Webster)	–	+	+	+	+	–	–	+	Second
Kirkpatrick 2001 (rat; F344; 58–1,527 ppm)	++	+	++	++	++	++	++	++	First
Takahara 1986a (mouse)	–	+	–	+	+	–	–	+	Second

Table C-8. Summary of Risk of Bias Assessment for 1,1,2-Trichloroethane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	
Oral acute exposure									
Platt and Cockrill 1969 (rat; Wistar-derived)	+	+	+	+	+	–	–	+	Second
Tyson et al. 1983 (rat; Sprague-Dawley)	–	+	+	+	+	–	+	+	First
White et al. 1985 (mouse; CD-1; 14 days)	+	+	++	+	++	+	++	++	First
Wright and Schaffer 1932 (dog)	– –	+	–	+	+	+	–	+	Second
Xia and Yu 1992 (rat; Wistar)	+	+	–	+	–	+	–	+	Second
Inhalation intermediate exposure									
Kirkpatrick 2002 (rat; F344)	++	++	++	++	++	++	++	++	First
Oral intermediate exposure									
White et al. 1985 (mouse; CD-1)	+	+	++	+	++	+	+	++	First
Oral chronic exposure									
NCI 1978 (rat; Osborne-Mendel)	+	+	++	+	+	++	++	++	First
NCI 1978 (mouse; B6C3F1)	+	+	++	+	+	++	++	++	First
Outcome: Neurological effects									
Inhalation acute exposure									
Bonnet et al. 1980 (rat; Sprague-Dawley)	–	+	+	+	–	–	–	+	Second
De Ceaurriz et al. 1981 (mouse; Swiss OF_1)	–	+	+	+	–	+	–	+	Second
Gehring 1968 (mouse; Swiss-Webster)	–	+	+	+	+	–	–	+	Second
Lazarew 1929 (mouse)	–	+	+	+	–	–	–	+	Second

APPENDIX C

Table C-8. Summary of Risk of Bias Assessment for 1,1,2-Trichloroethane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	Risk of bias tier
Kirkpatrick 2001 (rat; F344; 58–1,527 ppm)	++	+	++	++	++	++	++	++	First
Kirkpatrick 2001 (rat; F344; 45–1,474 ppm)	++	+	++	++	++	++	++	++	First
Oral acute exposure									
Beck 2004 (rat; Crl:CD(SD)IGS)	++	++	++	++	++	++	++	++	First
Borzelleca 1983 (mouse; CD-1)	–	+	+	+	–	–	–	+	Second
Kallman et al. 1983 (mouse; CD-1)	+	+	++	+	++	++	+	++	First
Kallman and Kaempf 1984 (mouse; CD-1)	+	+	++	+	++	++	+	++	First
White et al. 1985 (mouse; CD-1; once)	+	+	++	+	+	+	+	++	First
Wright and Schaffer 1932 (dog)	– –	+	–	+	+	+	–	+	Second
Oral intermediate exposure									
Maurissen et al. 2005 (rat; F344/DUCRL)	++	++	++	++	++	++	++	++	First
Oral chronic exposure									
NCI 1978 (rat; Osborne-Mendel)	+	+	++	+	+	++	++	++	First
NCI 1978 (mouse; B6C3F1)	+	+	++	+	+	++	++	++	First

APPENDIX C

Table C-8. Summary of Risk of Bias Assessment for 1,1,2-Trichloroethane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	Risk of bias tier
Outcome: Immunological effects									
Oral acute exposure									
Sanders et al. 1985 (mouse; CD-1)	+	+	++	+	++	+	++	++	First
Oral intermediate exposure									
Sanders et al. 1985 (mouse; CD-1)	+	+	++	+	++	+	++	++	First
Oral chronic exposure									
NCI 1978 (rat; Osborne-Mendel)	+	+	++	+	+	++	++	++	First
NCI 1978 (mouse; B6C3F1)	+	+	++	+	+	++	++	++	First

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 1,1,2-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 1,1,2-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 in Distiller, 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-9, C-10, and C-11, 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-9. 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-10. 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-11. 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 respiratory, hepatic, neurological, and immunological effects observed in animal experimental studies are presented in Table C-12.

A summary of the initial confidence ratings for each outcome is presented in Table C-13. 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-13.

Table C-12. Presence of Key Features of Study Design for 1,1,2-Trichloroethane—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Key feature: Sufficient number of animals per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
Outcome: Respiratory effects					
Inhalation acute exposure					
Kirkpatrick 2001 (rat; F344; 58–1,527 ppm)	Yes	No	Yes	Yes	High
Kirkpatrick 2001 (rat; F344; 45–1,474 ppm)	Yes	No	Yes	Yes	High
Oral acute exposure					
White et al. 1985 (mouse; CD-1; 14 days)	Yes	Yes	No	Yes	Moderate
Inhalation intermediate exposure					
Kirkpatrick 2002 (rat; F344 CDF Crl:BR)	Yes	Yes	Yes	Yes	High
Oral intermediate exposure					
White et al. 1985 (mouse; CD-1)	Yes	Yes	No	Yes	Moderate
Oral chronic exposure					
NCI 1978 (rat; Osborne-Mendel)	Yes	Yes	Yes	Yes	High
NCI 1978 (mouse; B6C3F1)	Yes	Yes	Yes	Yes	High
Outcome: Hepatic effects					
Inhalation acute exposure					
Carlson 1973 (rat; albino)	Yes	Yes	No	Yes	Moderate
Gehring 1968 (mouse; Swiss Webster)	No	Yes	No	No	Very Low
Kirkpatrick 2001 (rat; F344; 58–1,527 ppm)	Yes	No	Yes	Yes	High
Takahara 1986a (mouse)	No	Yes	No	No	Very Low
Oral acute exposure					
Platt and Cockrill 1969 (rat; Wistar-derived)	Yes	Yes	No	Yes	Moderate
Tyson et al. 1983 (rat; Sprague-Dawley)	No	No	No	No	Very Low
White et al. 1985 (mouse; CD-1; 14 days)	Yes	Yes	Yes	Yes	High
Wright and Schaffer 1932 (dog)	No	No	Yes	No	Very Low
Xia and Yu 1992 (rat; Wistar)	Yes	No	Yes	Yes	Moderate
Inhalation intermediate exposure					
Kirkpatrick 2002 (rat; F344)	Yes	Yes	Yes	Yes	High
Oral intermediate exposure					
White et al. 1985 (mouse; CD-1)	Yes	Yes	Yes	Yes	High
Oral chronic exposure					
NCI 1978 (rat; Osborne-Mendel)	Yes	Yes	Yes	Yes	High
NCI 1978 (mouse; B6C3F1)	Yes	Yes	Yes	Yes	High

Table C-12. Presence of Key Features of Study Design for 1,1,2-Trichloroethane—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Key feature: Sufficient number of animals per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
Outcome: Neurological effects					
Inhalation acute exposure					
Bonnet et al. 1980 (rat; Sprague-Dawley)	No	Yes	Yes	No	Low
De Ceaurriz et al. 1981 (mouse; Swiss OF_1)	No	Yes	No	No	Very Low
Gehring 1968 (mouse; Swiss-Webster)	No	Yes	No	No	Very Low
Lazarew 1929 (mouse)	No	No	No	No	Very Low
Kirkpatrick 2001 (rat; F344; 58–1,527 ppm)	Yes	No	Yes	Yes	High
Kirkpatrick 2001 (rat; F344; 45–1,474 ppm)	Yes	No	Yes	Yes	High
Oral acute exposure					
Beck et al. 2004	Yes	Yes	Yes	Yes	High
Borzelleca 1983 (mouse; CD-1)	No	No	Yes	No	Very Low
Kallman et al. 1983 (mouse; CD-1)	Yes	Yes	No	Yes	Moderate
Kallman and Kaempf 1984 (mouse; CD-1)	Yes	No	No	No	Low
White et al. 1985 (mouse; CD-1; once)	No	Yes	Yes	No	Low
Wright and Schaffer 1932 (dog)	No	No	Yes	No	Very Low
Oral intermediate exposure					
Maurissen et al. 2005 (rat; F344/DUCRL)	Yes	Yes	Yes	Yes	High
Oral chronic exposure					
NCI 1978 (rat; Osborne-Mendel)	Yes	Yes	No	Yes	Moderate
NCI 1978 (mouse; B6C3F1)	Yes	Yes	No	Yes	Moderate
Outcome: Immunological effects					
Oral acute exposure					
Sanders et al. 1985 (mouse; CD-1)	Yes	Yes	Yes	Yes	High
Oral intermediate exposure					
Sanders et al. 1985 (mouse; CD-1)	Yes	Yes	Yes	Yes	High
Oral chronic exposure					
NCI 1978 (rat; Osborne-Mendel)	Yes	Yes	No	Yes	Moderate
NCI 1978 (mouse; B6C3F1)	Yes	Yes	No	Yes	Moderate

Table C-13. Initial Confidence Rating for 1,1,2-Trichloroethane Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Respiratory effects		
Inhalation acute exposure		
Kirkpatrick 2001 (rat; F344; 58–1,527 ppm)	High	High
Kirkpatrick 2001 (rat; F344; 45–1,474 ppm)	High	
Inhalation intermediate exposure		
Kirkpatrick 2002 (rat; F344 CDF Crl:BR)	High	High
Oral acute exposure		
White et al. 1985 (mouse; CD-1)	Moderate	Moderate
Oral intermediate exposure		
White et al. 1985 (mouse; CD-1)	Moderate	Moderate
Oral chronic exposure		
NCI 1978 (rat; Osborne-Mendel)	High	High
NCI 1978 (mouse; B6C3F1)	High	
Outcome: Hepatic effects		
Inhalation acute exposure		
Carlson 1973 (rat; albino)	Moderate	High
Gehring 1968 (mouse; Swiss Webster)	Very Low	
Kirkpatrick 2001 (rat; F344; 58–1,527 ppm)	High	
Takahara 1986a (mouse)	Very Low	
Inhalation intermediate exposure		
Kirkpatrick 2002 (rat; F344)	High	High
Oral acute exposure		
Platt and Cockrill 1969 (rat; Wistar-derived)	Moderate	High
Tyson et al. 1983 (rat; Sprague-Dawley)	Very Low	
White et al. 1985 (mouse; CD-1)	High	
Wright and Schaffer 1932 (dog)	Very Low	
Xia and Yu 1992 (rat; Wistar)	Moderate	
Intermediate inhalation exposure		
Kirkpatrick 2002 (rat; F344 CDF Crl:BR)	High	High
Oral intermediate exposure		
White et al. 1985 (mouse; CD-1)	High	High
Oral chronic exposure		
NCI 1978 (rat; Osborne-Mendel)	High	High
NCI 1978 (mouse; B6C3F1)	High	
Outcome: Neurological effects		
Inhalation acute exposure		
Bonnet et al. 1980 (rat; Sprague-Dawley)	Low	High
De Ceaurriz et al. 1981 (mouse; Swiss OF_1)	Very Low	
Gehring 1968 (mouse; Swiss-Webster)	Very Low	
Lazarew 1929 (mouse)	Very Low	
Kirkpatrick 2001 (rat; F344; 58–1,527 ppm)	High	
Kirkpatrick 2001 (rat; F344; 45–1,474 ppm)	High	

Table C-13. Initial Confidence Rating for 1,1,2-Trichloroethane Health Effects Studies

	Initial study confidence	Initial confidence rating
Oral acute exposure		
Beck 2004 (rat; Crl:CD(SD)IGS)	High	High
Borzelleca 1983 (mouse; CD-1)	Very Low	
Kallman et al. 1983 (mouse; CD-1)	Moderate	
Kallman and Kaempf 1984 (mouse; CD-1)	Low	
White et al. 1985 (mouse; CD-1)	Low	
Wright and Schaffer 1932 (dog)	Very Low	
Oral intermediate exposure		
Maurissen et al. 2005 (rat; F344/DUCRL)	High	High
Oral chronic exposure		
NCI 1978 (rat; Osborne-Mendel)	Moderate	Moderate
NCI 1978 (mouse; B6C3F1)	Moderate	
Outcome: Immunological effects		
Oral acute exposure		
Sanders et al. 1985 (mouse; CD-1)	High	High
Oral intermediate exposure		
Sanders et al. 1985 (mouse; CD-1)	High	High
Oral chronic exposure		
NCI 1978 (rat; Osborne-Mendel)	Moderate	Moderate
NCI 1978 (mouse; B6C3F1)	Moderate	

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 respiratory, hepatic, neurological, and immunological effects are presented in Table C-14. 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 1,1,2-trichloroethane exposure is presented in Table C-15.

Table C-14. Adjustments to the Initial Confidence in the Body of Evidence

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Outcome: Respiratory effects			
Animal studies	High	None	High
Outcome: Hepatic effects			
Animal studies	High	None	High
Outcome: Neurological effects			
Animal studies	High	None	High
Outcome: Immunological effects			
Animal studies	High	-1 unexplained inconsistency	Moderate

Table C-15. Confidence in the Body of Evidence for 1,1,2-Trichloroethane

	Confidence in body of evidence	
Outcome	Human studies	Animal studies
Respiratory effects	No data	High
Hepatic effects	No data	High
Neurological effects	No data	High
Immunological effects	No data	Moderate

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 (Table C-8). 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 1,1,2-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 1,1,2-trichloroethane is presented in Table C-16.

Table C-16. Level of Evidence of Health Effects for 1,1,2-Trichloroethane

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Animal studies			
Respiratory effects following inhalation exposure	High	Health effect	High
Hepatic effects	High	Health effect	High
Neurological effects	High	Health effect	High
Immunological effects	Moderate	Health effect	Moderate

C.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

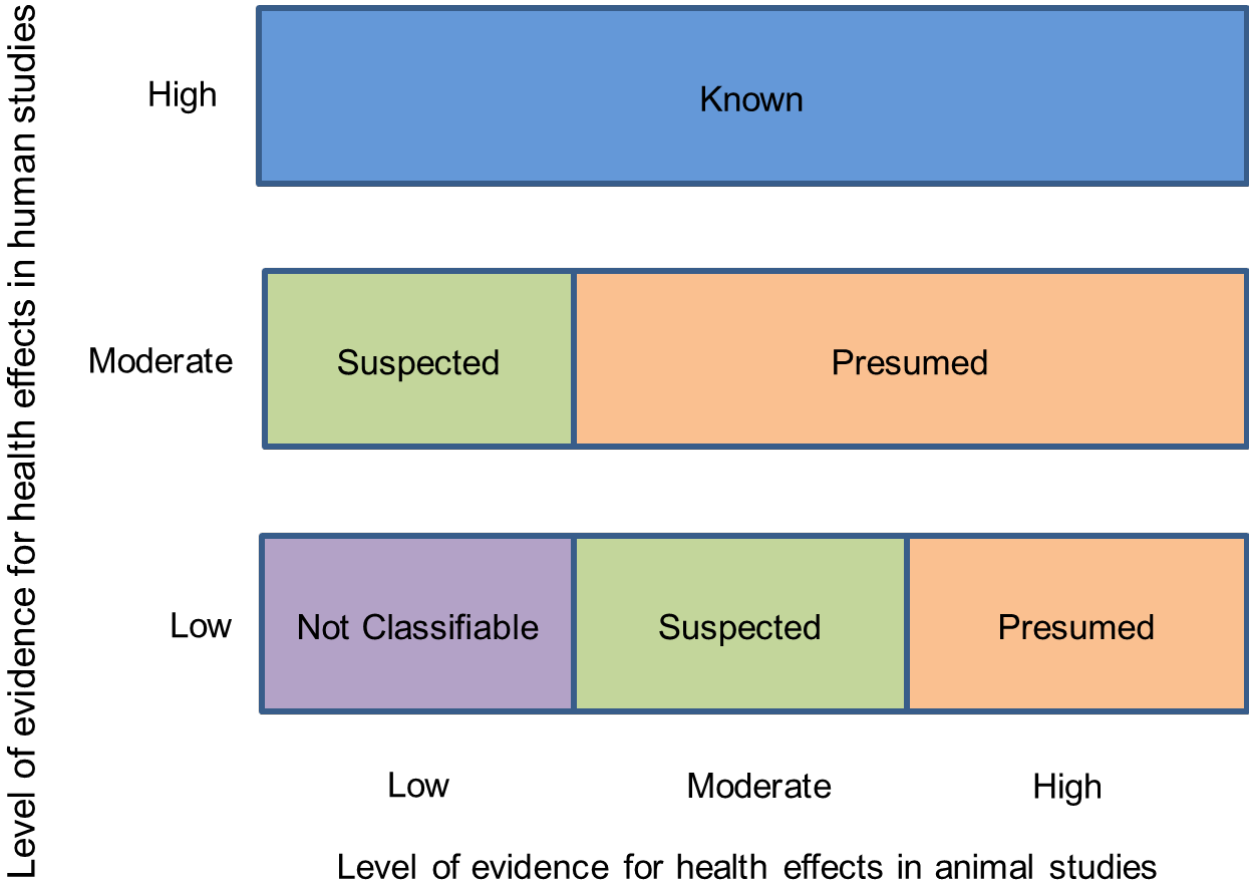
The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. For health effects, there were four hazard identification conclusion categories:

- **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

Figure C-1. Hazard Identification Scheme



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.

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 1,1,2-trichloroethane are listed below and summarized in Table C-17.

Presumed Health Effects

- Respiratory effects following inhalation exposure
  - No human data
  - Acute- and intermediate-duration inhalation studies identified changes in the bronchoalveolar lavage fluid (increased protein content) and nasal lesions (vacuolization and microcyst formation, respiratory epithelial metaplasia, atrophy, and/or necrosis of the olfactory epithelium) in male and female rats (Kirkpatrick 2001, 2002).
- Hepatic effects
  - No human data
  - Liver effects (namely increased ALT and/or AST, increased liver weight, and/or histopathological changes including hepatocellular vacuolization and necrosis, fatty changes, and/or swelling) were identified in numerous acute- and intermediate-duration toxicity studies (via the inhalation and oral routes of exposure; Carlson 1973; Gehring 1968; Kirkpatrick 2001, 2002; Moody et al. 1981; Takahara 1986c; Tyson et al. 1983; unpublished data from Dow Chemical Co. as provided in Torkelson and Rowe 1981; White et al. 1985). However, liver lesions were not reported in rats and mice orally exposed to 1,1,2-trichloroethane for 78 weeks (NCI 1978).
- Neurological effects
  - No human data
  - Acute-duration inhalation toxicity studies in rats and mice predominantly identified clinical signs of neurotoxicity at sublethal exposure concentrations (Bonnet et al. 1980; De Ceaurriz et al. 1981; Gehring 1968; Kirkpatrick 2001; Lazarew 1929). In addition to clinical signs, reduced motor activity, gait impairment, and taste aversion (to saccharin) were observed in acute-duration oral toxicity studies in rats and mice (Beck 2004; Borzelleca 1983; Kallman et al. 1983). However, rats treated for up to 13 weeks with 1,1,2-trichloroethane in drinking water showed no effects on FOB tests or histopathology of nervous system organs and tissues (Maurissen et al. 2005). Likewise, there was no evidence of neurological effects (based on histopathology) in rats and mice treated orally with 1,1,2-trichloroethane for 78 weeks. Few repeated-dose studies have evaluated neurobehavioral effects (NCI 1978).

Suspected Health Effect

- Immunological effects
  - No human data
  - An intermediate-duration oral toxicity study identified a dose-related reduction in hemagglutination titers in male and female mice (Sanders et al. 1985). However, other immunological parameters (numbers of splenic antibody-forming cells, the response of splenic lymphocytes to mitogens, and macrophage activity) evaluated in the same study were not consistently affected. In addition, mice exposed to 1,1,2-trichloroethane for 14 days showed no significant, treatment-related immunological effects (based on similar humoral or cell-mediated immune response evaluations; Sanders et al. 1985). Chronic-duration studies in rats and mice identified NOAELs for immunological effects based on the absence of histopathological changes in the spleen, thymus, bone marrow, or lymph nodes; immunological function was not evaluated in these studies (NCI 1978).

Table C-17. Hazard Identification Conclusions for 1,1,2-Trichloroethane

Outcome	Hazard identification
Respiratory effects	Presumed health effect
Hepatic effects	Presumed health effect
Neurological effects	Presumed health effect
Immunological effects	Suspected health effect

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), behavioral (BH), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), enzyme activity (EA), food intake (FI), fetal toxicity (FX), gross necropsy (GN), hematology (HE), histopathology (HP), lethality (LE), maternal toxicity (MX), organ function (OF), ophthalmology (OP), organ weight (OW), teratogenicity (TG), 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.

(13) 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.

(14) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints appear in the LSE table.

(15) Levels of exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) 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).

(17) 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.

(18) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

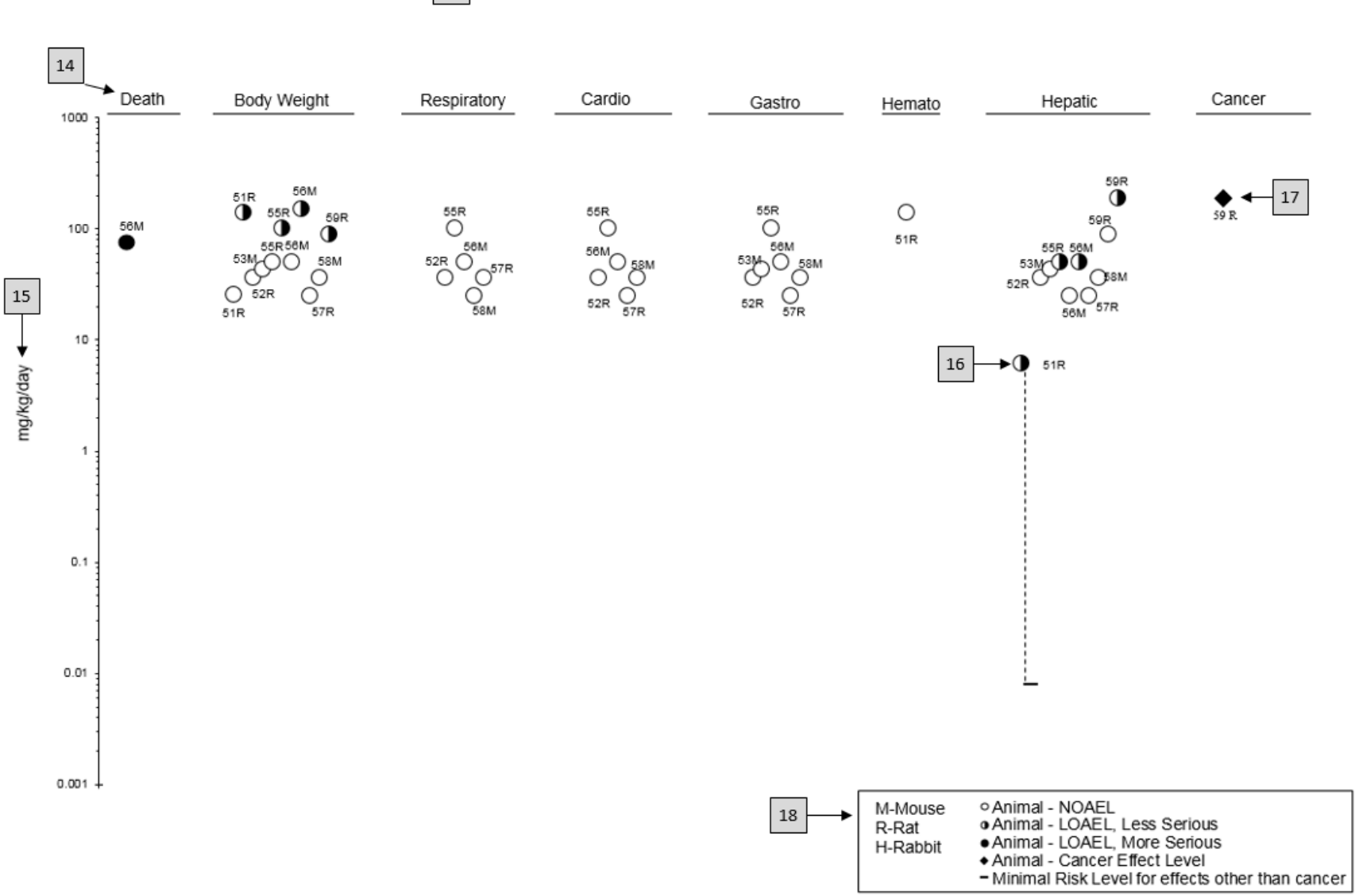
APPENDIX D

Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral (1)

Figure key[a] (2)	Species (strain) No./group (3)	Exposure parameters (4)	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).

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

The following additional materials are available online:

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

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.asp). Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: https://www.cdc.gov/nceh/.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: https://www.niehs.nih.gov/.

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 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 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.

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 Substance 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	lactic 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 level/limit
REL-C	recommended exposure level-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
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