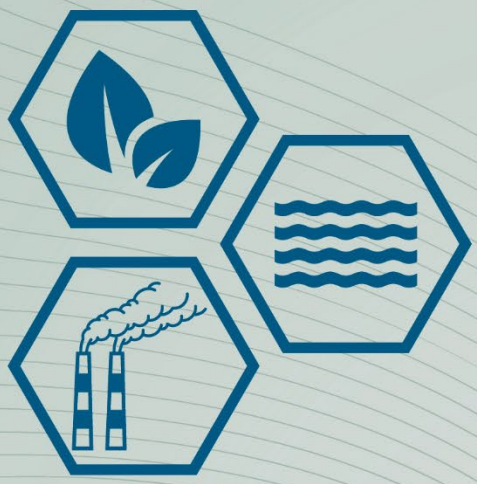


Toxicological Profile for 1,2-Dichloroethene

Draft for Public Comment

August 2023

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

CS274127-A

DISCLAIMER

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

This information is distributed solely for the purpose of pre dissemination public comment under applicable information quality guidelines. It has not been formally disseminated by the Agency for Toxic Substances and Disease Registry. It does not represent and should not be construed to represent any agency determination or policy.

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
Office of Innovation and Analytics
Toxicology Section
1600 Clifton Road, N.E.
Mail Stop S106-5
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, 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.

Aaron Bernstein, M.D., M.P.H.
Director, National Center for Environmental Health and
Agency for Toxic Substances and Disease Registry,
Centers for Disease Control and Prevention

Christopher M. Reh, Ph.D.
Associate Director
Agency for Toxic Substances and Disease Registry
Centers for Disease Control and Prevention

VERSION HISTORY

Date	Description
August 2023	Draft for public comment toxicological profile released
August 1996	Final toxicological profile released

CONTRIBUTORS & REVIEWERS

CHEMICAL MANAGER TEAM

Malcolm Williams, D.V.M., Ph.D. (Lead)
Gaston Casillas, Ph.D.
Sam Keith, M.S., C.H.P.
Mike Fay, Ph.D.

ATSDR, Office of Innovation and Analytics, Toxicology Section, Atlanta, GA

Julie M. Klotzbach, Ph.D.
Mario Citra, Ph.D.

SRC, Inc., North Syracuse, NY

REVIEWERS

Interagency Minimal Risk Level Workgroup:

Includes ATSDR; National Center for Environmental Health (NCEH); National Institute for Occupational Safety and Health (NIOSH); U.S. Environmental Protection Agency (EPA); National Toxicology Program (NTP).

Additional reviews for science and/or policy:

ATSDR, Office of Community Health Hazard Assessment; ATSDR, Office of Capacity Development and Applied Prevention Science; ATSDR, Office of Science; NCEH, Division of Laboratory Sciences; NCEH, Division of Environmental Health Science and Practice; EPA.

PEER REVIEWERS

1. Mary Beth Genter, Ph.D; Professor; Department of Environmental Health; University of Cincinnati; Cincinnati, Ohio.

2. Matt Simcik, Ph.D.; Professor; Division of Environmental Health Sciences; School of Public Health; University of Minnesota; Minneapolis, Minnesota.

3. G.A. Shakeel Ansari, Ph.D.; Professor; Department of Pathology; University of Texas Medical Branch; Galveston, Texas.

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

1,2-Dichloroethene is a volatile, low molecular weight halogenated liquid that is used as a chemical intermediate or an industrial solvent. Although 1,2-dichloroethene is often referred to as a single chemical, it exists as two geometric isomers that have distinct properties.

When 1,2-dichloroethene is released to the environment, most will quickly end up as a gas in the atmosphere. Once in the atmosphere, it will break down by reactions with substances in the air. When released to lakes, rivers, and other bodies of water, most of it evaporates into the air. When released to soil, it also volatilizes to air but its high leachability indicates that it may migrate to groundwater.

Most studies indicate that both isomers of 1,2-dichloroethene are highly resistant to biodegradation in an aerobic environment but may biodegrade under anaerobic conditions. Biodegradation of 1,2-dichloroethene can produce vinyl chloride, which is a hazardous chemical substance. Based on the high measured vapor pressure and large estimated Henry's law constant, volatilization of 1,2-dichloroethene from water is expected to be an important fate process.

Exposure to 1,2-dichloroethene originates from primarily anthropogenic sources. Since 1,2-dichloroethene is a volatile liquid at room temperature, the most likely route of exposure would be from breathing air containing 1,2-dichloroethene. Occurrences of 1,2-dichloroethene in air can be attributed to releases from factories that manufacture or use 1,2-dichloroethene and/or evaporation from some landfills, solvents, and refrigerants.

Occupational exposure to trans- and cis-1,2-dichloroethene is most likely to occur through inhalation and dermal routes. The general population is most likely exposed by inhalation of contaminated air and ingestion of contaminated food and drinking water.

1.2 SUMMARY OF HEALTH EFFECTS

For this profile, toxicity studies for 1,2-dichloroethene are categorized by isomer composition: trans-1,2-dichloroethene; cis-1,2-dichloroethene; and mixtures of the cis- and trans- isomers. Only a few studies investigating health effects from exposure to 1,2-dichloroethene in humans were identified, with

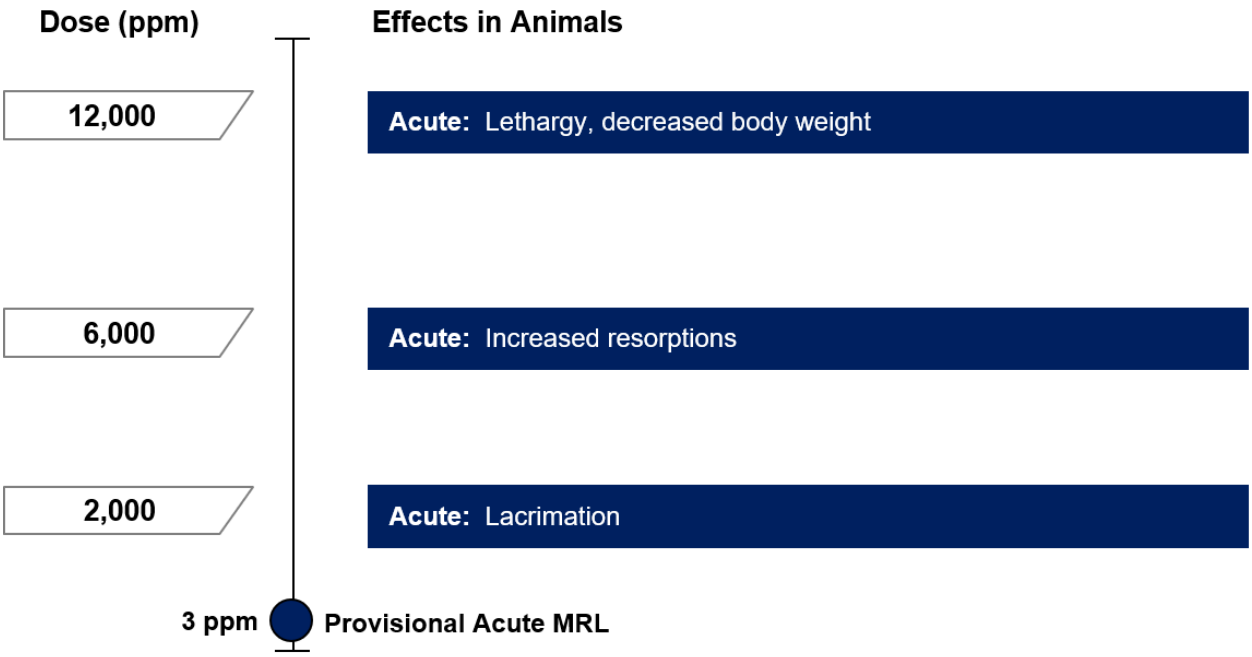
data limited to studies on trans-1,2-dichloroethene. Information on the health effects in experimental animals is available as follows:

- trans-1,2-dichloroethene: acute- and intermediate-duration oral and inhalation exposures and acute-duration dermal exposure;
- cis-1,2-dichloroethene: acute-duration inhalation exposure and acute- and intermediate-duration oral exposures; and
- mixtures of cis- and trans-1,2-dichloroethene: acute-duration inhalation exposure and acute- and intermediate-duration oral exposures.

No studies on chronic-duration exposure to trans-1,2-dichloroethene, cis-1,2-dichloroethene, or mixtures of cis- and trans- isomers were identified for any exposure route in animals.

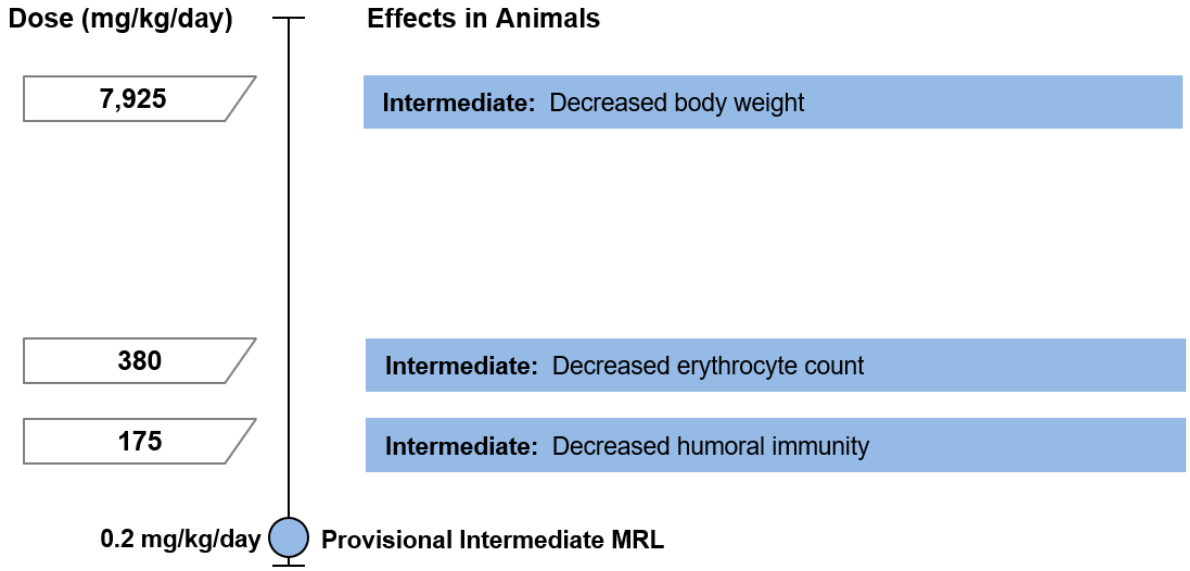
For trans-1,2-dichloroethene, the most sensitive effect of acute-duration inhalation exposure is contact irritation of the eye (lacrimation), and the most sensitive effect of intermediate-duration oral exposure is the immune system (decreased humoral immunity), as shown in Figures 1-1 and 1-2, respectively. Dermal exposure studies also indicate that trans-1,2-dichloroethene can damage the skin. ATSDR conducted a systematic review assessing ocular irritation and decreased immune function. Studies on cis-1,2-dichloroethene and mixtures of cis- and trans-1,2-dichlorothene did not identify toxicologically significant effects at sublethal levels.

Figure 1-1. Health Effects Found in Animals Following Inhalation Exposure to trans-1,2-Dichloroethene*



*No intermediate- or chronic-duration MRLs were derived for trans-1,2-dichloroethene

Figure 1-2. Health Effects Found in Animals Following Oral Exposure to trans-1,2-Dichloroethene*



*No acute- or chronic-duration MRLs were derived for trans-1,2-dichloroethene

Information on the most sensitive effects of trans-1,2-dichloroethene is summarized as follows.

Ocular Effects. Exposure to trans-1,2-dichloroethene in air and by instillation into the eye produces ocular irritation. In pregnant rats exposed by whole-body inhalation for 10 days, lacrimation was observed at concentrations of 2,000, 6,000, and 12,000 ppm (Hurtt et al. 1993). Brown, periocular staining, due to excessive lacrimation, was observed in the 6,000 ppm (18/24) and 12,000 ppm (22/24) exposure groups. Instillation of 0.01 trans-1,2-dichloroethene to the eyes of rabbits for 20 seconds resulted in transient severe corneal opacity, moderate iritis, and conjunctivitis (DuPont 1988c).

Immunological Effects. Immunological function has been assessed in acute- and intermediate-duration oral exposure studies (Munson et al. 1982; Shopp et al. 1985). Humoral immunity, as measured by the number of spleen IgM antibody-forming cells (AFCs) directed against sheep red blood cells (sRBCs), was decreased in mice following oral exposure to trans-1,2-dichloroethene at doses of 17, 175, and 387 mg/kg/day for 90 days (Shopp et al. 1985). Cellular immune function was not affected. No additional intermediate-duration oral exposure studies evaluating immune studies were identified. No effects on humoral or cellular immunity were observed in acute-duration oral studies in mice at doses up to 220 mg/kg/day for 14 days (Munson et al. 1982; Shopp et al. 1985).

Other effects observed in laboratory animals exposed to trans-1,2-dichloroethene are summarized below, although these effects do not appear to be sensitive targets.

Body Weight Effects. Conflicting results have been observed regarding decreased body weight and body weight gain. Maternal body weight gain was reduced in pregnant rats exposed via inhalation to 12,000 ppm trans-1,2-dichloroethene during gestation (Hurtt et al. 1993), although body weight was similar to controls at the end of pregnancy. In contrast, no effect on body weight was observed in male or female rats following inhalation of 4,000 ppm trans-1,2-dichloroethene for 90 days (DuPont 1998). Body weight was also decreased in female rats following dietary exposure to 7,928 mg/kg/day for 14 weeks. Other studies found no effects of oral acute-duration exposures to trans-1,2-dichloroethene in rats or mice at maximum oral doses tested of 210–220 mg/kg/day (Barnes et al. 1985; Munson et al. 1982) or 387–8,065 mg/kg/day (Barnes et al. 1985; Hayes et al. 1987; NTP 2002), respectively.

Hematological Effects. Results of studies of effects of trans-1,2-dichloroethene on hematological parameters are inconsistent. Small, dose-related decreases in erythrocyte counts were observed in male and female rats exposed to dietary trans-1,2-dichloroethene for 14 weeks at doses of 380, 770, 1,540, and 3,210 mg/kg/day (NTP 2002). In female rats, erythrocyte counts were decreased in the 1,580 and 3,245 mg/kg/day exposure groups. However, other oral exposure studies did not observe adverse hematological effects following acute-duration exposure of rats and mice to maximum doses of 210–8,065 mg/kg/day (Barnes et al. 1985; Hayes et al. 1987; NTP 2002) or in a 90-day drinking water study at doses up to 2,809 and 3,114 mg/kg/day in male and female rats, respectively (Hayes et al. 1987). In addition, no hematological effects were observed in rats exposed to 4,000 ppm for 90 days by inhalation (DuPont 1998).

Neurological Effects. Little information on neurological effects of trans-1,2-dichloroethene is available. At sublethal levels, narcosis (incidence data not reported) was observed in rats exposed by inhalation on gestation days (GDs) 7–16 at concentrations of 6,000 and 12,000 ppm, but not at 2,000 ppm (Hurtt et al. 1993). Lethargy was observed in rats exposed to 12,000 ppm, but not at lower exposure concentrations (Hurtt et al. 1993). In single-dose oral lethality studies in rats, clinical signs of neurotoxicity (central nervous system depression, decreased activity, ataxia, loss of righting reflex, and depressed respiration) have been observed (Barnes et al. 1985; Hayes et al. 1987); however, due to the lack of incidence data, reliable no-observed-adverse-effect level (NOAEL) and lowest-observed-adverse-effect level (LOAEL) values could not be identified. No neurotoxicity (assessed by functional observational batteries, cage-side evaluations for clinical signs, and histopathology of neurological tissues) was observed in male and female rats at maximum doses of 3,210 and 3,245 mg/kg/day, respectively, or in male and female mice at maximum doses of 8,065 and 7,925 mg/kg/day, respectively, in a 14-week dietary study.

Developmental Effects. An epidemiological study did not find associations between maternal exposure to trans-1,2-dichloroethene during pregnancy and birth defects (neural tube defect or oral cleft defects (Ruckart et al. 2013). A gestational exposure study in rats observed increased resorptions following inhalation exposure to 6,000 ppm trans-1,2-dichloroethene and decreased fetal weight in females at 12,000 ppm (Hurtt et al. 1993). No additional developmental studies were identified for trans-1,2-dichloroethene.

1,2-Dichloroethene is not listed by Department of Health and Human Services (HHS) National Toxicology Program (NTP) in the 15th Report on Carcinogens (NTP 2021). The U.S. Environmental Protection Agency (EPA) has not classified the carcinogenicity of 1,2-dichloroethene due to inadequate

information (IRIS 2010a, 2010b). The International Agency for Research on Cancer (IARC) has not evaluated the carcinogenicity of 1,2-dichloroethene (IARC 2022).

1.3 MINIMAL RISK LEVELS (MRLs)

Development of MRLs was considered for the individual cis- and trans- isomers, but not for mixtures of the isomers. The database for trans-1,2-dichloroethene was considered adequate to derive an acute-duration inhalation MRL and an intermediate-duration oral MRL. The MRL values for trans-1,2-dichloroethene are summarized in Table 1-1. Data were not considered adequate for derivation of intermediate- and chronic-duration inhalation MRLs or acute- and chronic-duration oral MRLs for trans-1,2-dichloroethene. As presented in Figures 1-3 and 1-4, available data for trans-1,2-dichloroethene show that contact irritation of the eye and the immune system function are the most sensitive effects. The database for cis-1,2-dichloroethene was not considered adequate for derivation of inhalation or oral MRLs for any exposure duration (Table 1-2).

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

The eye is the most sensitive target of trans-1,2-dichloroethene inhalation exposure.
Numbers in circles are the lowest LOAELs for all health effects in animals; exposure data for humans are uncertain.

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

The immune system is the most sensitive target of trans-1,2-dichloroethene inhalation exposure. Numbers in circles are the lowest LOAELs for all health effects in animals; exposure data for humans are uncertain.

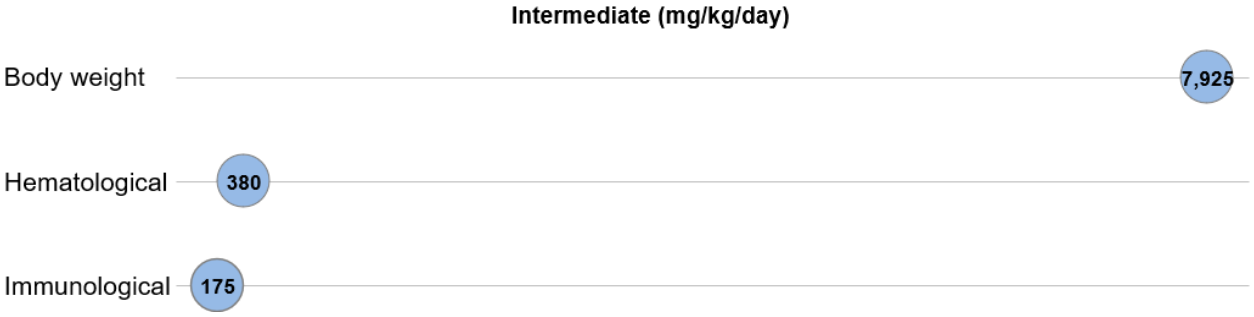


Table 1-1. Minimal Risk Levels (MRLs) for trans-1,2-Dichloroethene[a]

Exposure route	Exposure duration	Provisional MRL	Critical effect	POD type	POD value	Uncertainty/ modifying factor	Reference
Inhalation	Acute	**3 ppm** (12 mg/m^3)	Lacrimation	$BMCL_{10}$	256.47 ppm	UF: 100	Hurtt et al. 1993
	Intermediate	None	–	–	–	–	–
	Chronic	None	–	–	–	–	–
Oral	Acute	None	–	–	–	–	–
	Intermediate	**0.2 mg/kg/day**	Decreased humoral immunity	$BMDL_{1SD}$	16.75 mg/kg/day	UF: 100	Shopp et al. 1985
	Chronic	None	–	–	–	–	–

[a]See Appendix A for additional information.

$BMCL_{10}$ = 95% lower confidence limit on the benchmark concentration (subscripts denote benchmark response: i.e., 10 = dose associated with 10% extra risk); BMDL = 95% lower confidence limit on the benchmark dose; HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; POD = point of departure; SD = standard deviation; UF = uncertainty factor

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

No MRLs were derived for any exposure route or duration for cis-1,2-dichloroethene.

[a]See Appendix A for additional information.

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

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

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. Figures 2-1, 2-2, and 2-3 provide an overview of the database of studies in humans or experimental animals for trans-1,2-dichloroethene, cis-1,2-dichloroethene, and mixtures of cis- and trans-1,2-dichloroethene, respectively, included in this chapter of the profile. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to cis- and trans-1,2-dichloroethene and mixtures of cis- and trans-1,2-dichloroethene, 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 trans-1,2-dichloroethene was also conducted; the results of this review are presented in Appendix C.

Animal studies for trans-1,2-dichloroethene are presented in Table 2-1 and Figure 2-4 for inhalation exposure, Table 2-2 and Figure 2-5 for oral exposure, and Table 2-3 for dermal exposure. For cis-1,2-dichloroethene, oral studies are presented in Table 2-4 and Figure 2-6. For mixtures of cis-and trans-1,2-dichloroethene isomers, inhalation studies are presented in Table 2-5 and Figure 2-7. Note that only one study was identified for inhalation exposure to cis-1,2-dichloroethene and one study was identified for oral exposure to a mixture of the cis- and trans- isomers; therefore, summary tables and figures for these exposures were not developed.

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

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

For this profile, toxicity studies for 1,2-dichloroethene are categorized by isomer composition as follows: trans-1,2-dichloroethene; cis-1,2-dichloroethene; and mixtures of cis-and trans-dichloroethene.

trans-1,2-Dicloroethene. The toxicity of trans-1,2-dichloroethene has not been extensively studied. Only a few studies have evaluated toxicity to humans. Thus, available information regarding the health effects of trans-1,2-dichloroethene comes almost exclusively from studies in experimental animals. Studies include acute- and intermediate-duration inhalation and oral exposures. Studies have also assessed the effects of acute-duration dermal and ocular exposures. No chronic-duration studies were identified for any route of exposure. Available studies for trans-1,2-dichloroethene are depicted in Figure 2-1. Approximately half of the studies employed oral exposure. The most examined endpoints in inhalation and oral studies were lethality, hepatic, and immunological.

Based on animal data, the following targets of trans-1,2-dichloroethene were identified as follows.

Based on this review, immunological effects are a presumed health effect for humans.

- ***Ocular Effects.*** Ocular effects are a suspected health effect based on limited acute-duration exposure of rats to 1,2-dichloroethene in air. Exposure to trans-1,2-dichloroethene in air and by instillation into the eye produces ocular irritation. Dose-related lacrimation (indicating ocular irritation) was observed in an acute-duration, whole-body exposure study in pregnant rats. Ocular irritation and damage to the eyes were also observed in rabbits following instillation of trans-1,2-dichloroethene to the eyes.

- ***Immunological Effects.*** Immunological effects of 1,2-dichloroethene are a presumed health effect for humans based on limited evidence in mice. Decreased humoral immunity, but not cellular immunity, was observed following intermediate-duration oral exposure. No changes in immune function were observed in animal studies following acute-duration oral exposure.

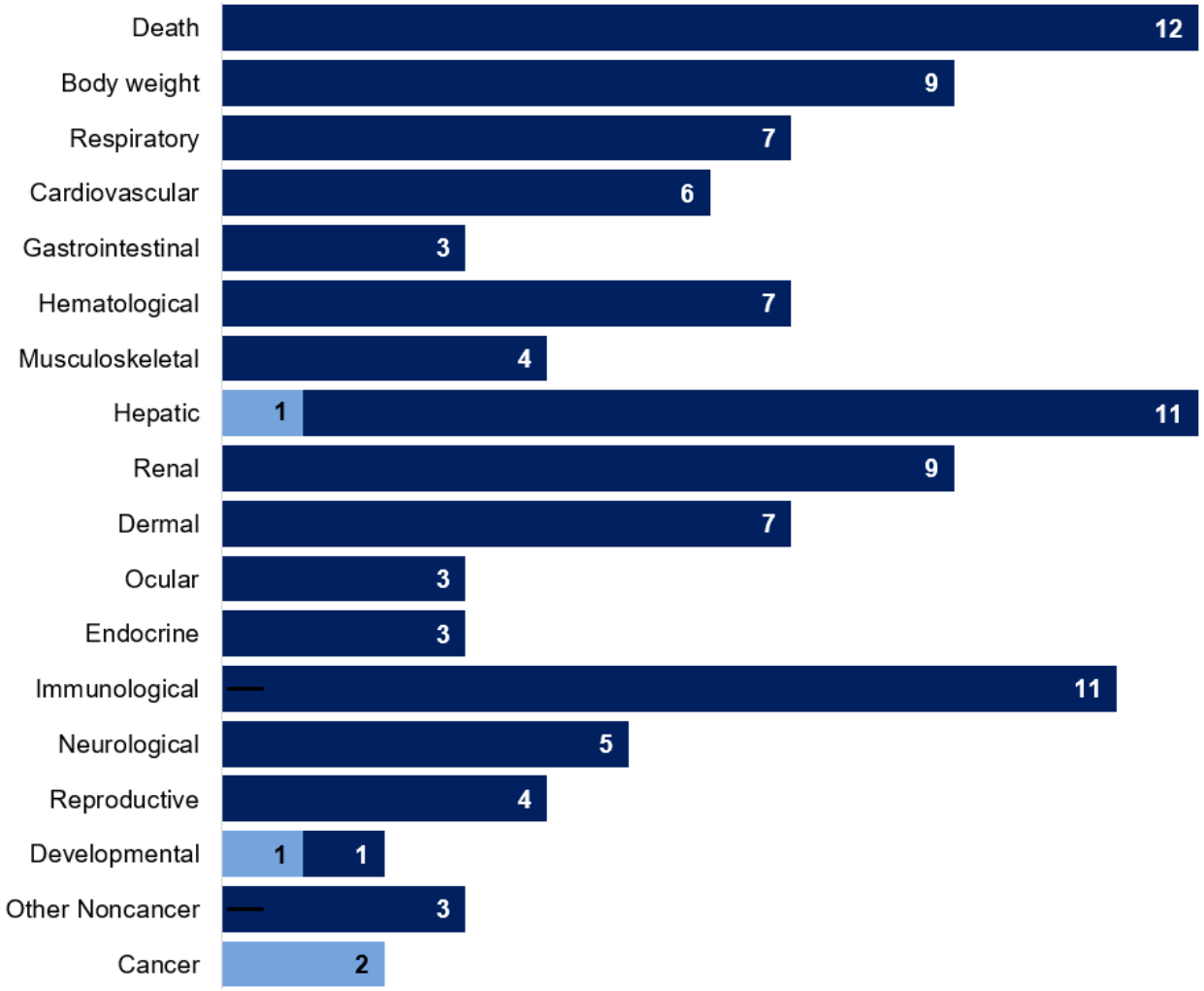
- ***Other Effects.*** Decreased body weight and hematological, developmental, and neurological effects have also been observed; however, these do not appear to be sensitive targets of trans-1,2-dichloroethene. Dermal exposure was irritating and damaging to the skin.

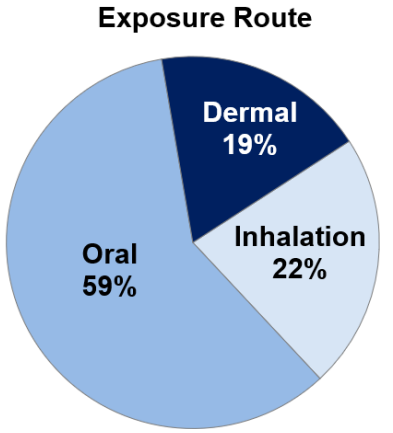
cis-1,2-Dichloroethene. No studies investigating the toxicity of cis-1,2-dichloroethene in humans were identified. Available studies for trans-1,2-dichloroethene in laboratory animals are depicted in Figure 2-2. Studies on the toxicity of cis-1,2-dichloroethene are limited to two studies in rats: one study evaluating acute-duration lethality following a single dose inhalation exposure; and an oral exposure study evaluating comprehensive toxicological endpoints in animals exposed for acute- and intermediate-durations. No chronic-duration studies for cis-dichloroethene in laboratory animals were identified for any exposure route. No sensitive targets of cis-dichloroethene have been identified, as no biologically significant effects have been observed at sublethal levels.

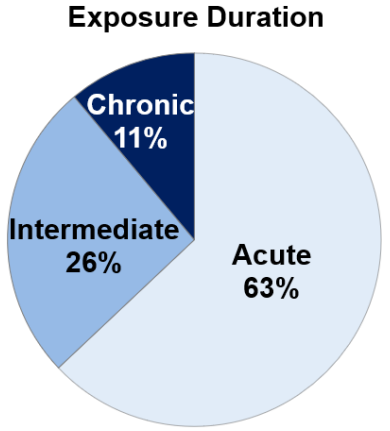
Mixtures of cis- and trans-1,2-Dichloroethene. The toxicity of mixtures of the cis- and trans-isomers has been investigated in acute- and intermediate-duration studies, with most studies providing information on acute lethality. These studies are shown in Figure 2-3. No sensitive targets for mixtures of cis- and trans-1,2-dichloroethene were identified at sublethal exposures.

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

Most studies examined lethality and potential hepatic and immune effects of trans-1,2-dichloroethene
Fewer studies evaluated health effects in humans than animals (counts represent studies examining endpoint)





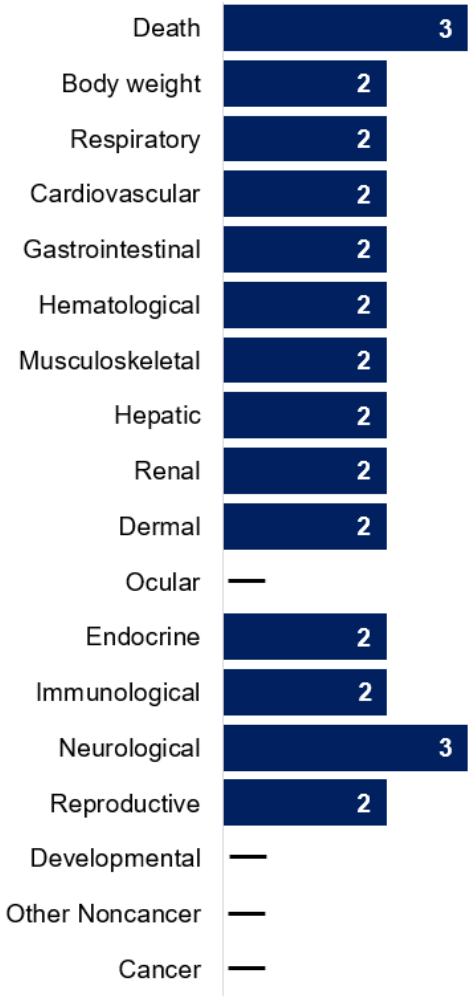


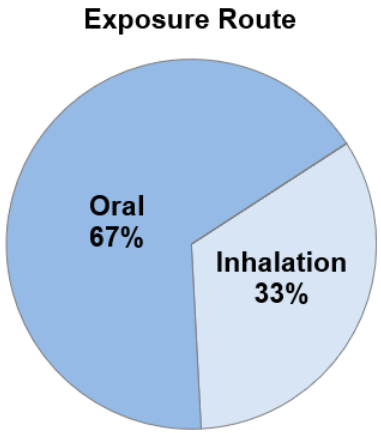
*Includes studies discussed in Chapter 2. A total of 27 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

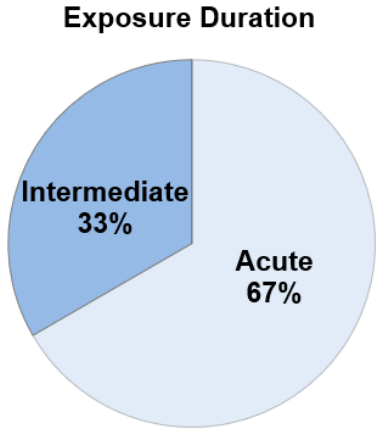
Figure 2-2. Overview of the Number of Studies Examining cis-1,2-Dichloroethene Health Effects*

Most studies examined lethality and potential hepatic and immune effects of cis-1,2-dichloroethene

The majority of the studies examined oral exposure in animals (counts represent studies examining endpoint); no data were identified for humans (counts represent studies examining endpoint)

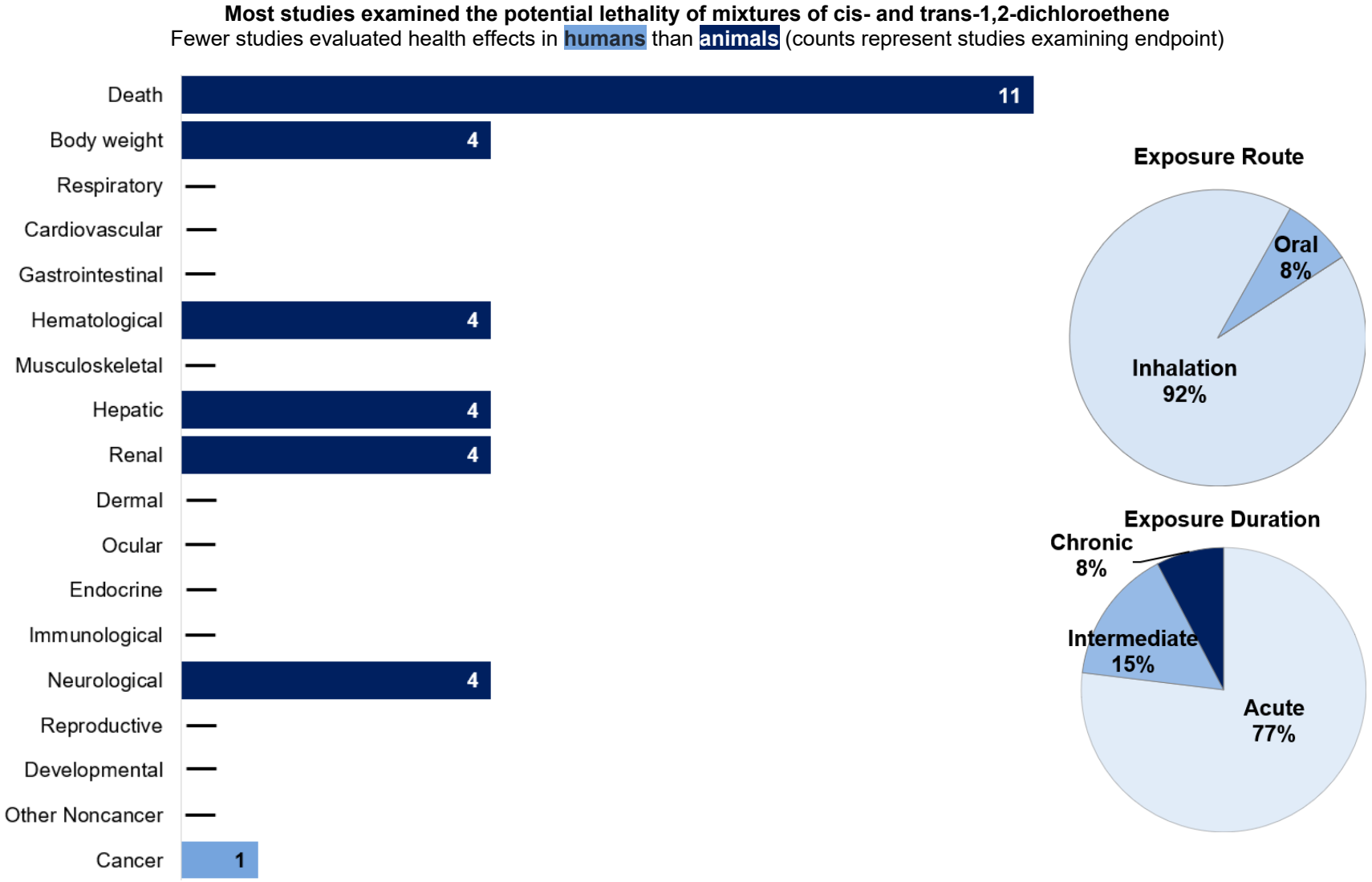






*Includes studies discussed in Chapter 2. A total of 3 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

Figure 2-3. Overview of the Number of Studies Examining Mixtures of trans- and cis-1,2-Dichloroethene Health Effects*



*Includes studies discussed in Chapter 2. A total of 13 studies (including those finding no effect) have examined toxicity; studies examined multiple endpoints.

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
Hurtt et al. 1993									
1	Rat (CD BR) 24 F	6 hours/day 10 days GDs 7–16	0, 2000, 6,000, 12,000	BW, CS, DX, FI, GN, LE, OW	Bd wt	6,000	12,000		Maternal weight gain was decreased by 33.8% at the end of the exposure period; body weight at the end of gestation was similar to control
					Ocular		2,000[b]		Lacrimation ($BMCL_{10}$ = 256.47)
					Neuro	6,000	12,000		Lethargy
					Develop	2,000	6,000		Increased resorptions
Gradiski et al. 1978									
2	Mouse (OF1, SPF) 20 F	6 hours		LE	Death			21,723	LC_{50}
INTERMEDIATE EXPOSURE									
DuPont 1998									
3	Rat (CD) 15 M, 15 F	6 hours/day 5 days/week 90 days	0, 200, 1,000, 4,000	BC, BW, CS, FI, GN, HE, HP, LE, NX, OP, UR	Bd wt	4,000			
					Resp	4,000			
					Cardio	4,000			
					Gastro	4,000			
					Hemato	4,000			
					Musc/skel	4,000			
					Hepatic	4,000			
					Renal	4,000			
					Dermal	4,000			
					Ocular	4,000			
					Endocr	4,000			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Immuno	1,000 F 4,000 M	4,000 M		Lymphocytes decreased by 26%
					Neuro	4,000			
					Repro	4,000			
					Other noncancer		4,000		Increased serum glucose

[a]The number corresponds to entries in Figure 2-4.
[b]Used to derive a provisional acute-duration inhalation MRL. Using BMD modeling, BMC_{10} and $BMCL_{10}$ values of 740.28 and 256.47 ppm, respectively, were calculated for lacrimation. The $BMCL_{10}$ was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability), resulting in a provisional acute-duration MRL of 3 ppm for trans-1,2-dichloroethene. See Appendix A for more detailed information regarding the provisional MRL.

BC = blood chemistry; Bd wt or BW = body weight; BMC = benchmark concentration; BMCL = lower 95% confidence limit on the benchmark concentration; BMC = benchmark dose; Cardio = cardiological; CS = clinical signs; Develop = developmental; DX = developmental toxicity; Endocr = endocrine; F = female(s); FI = food intake; Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; LC_{50} = median lethal concentration; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); MRL = Minimal Risk Level; Musc/skel = musculoskeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NX = neurotoxicity; OP = ophthalmological; Repro = reproductive; Resp = respiratory; UR = urinalysis

Figure 2-4. Levels of Significant Exposure to trans-1,2-Dichloroethene – Inhalation

Acute (≤14 days)

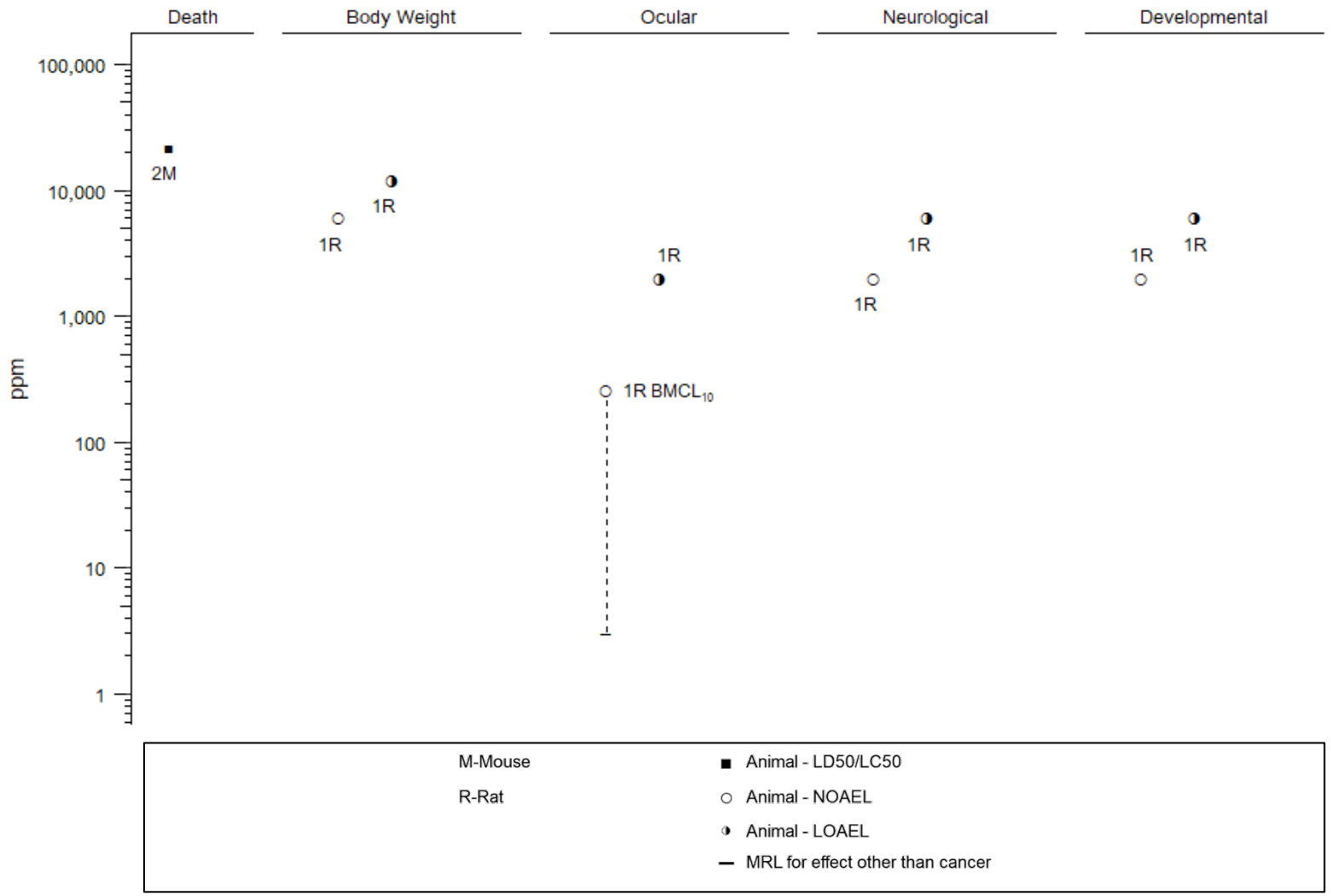


Figure 2-4. Levels of Significant Exposure to trans-1,2-Dichloroethene – Inhalation

Intermediate (15-364 days)

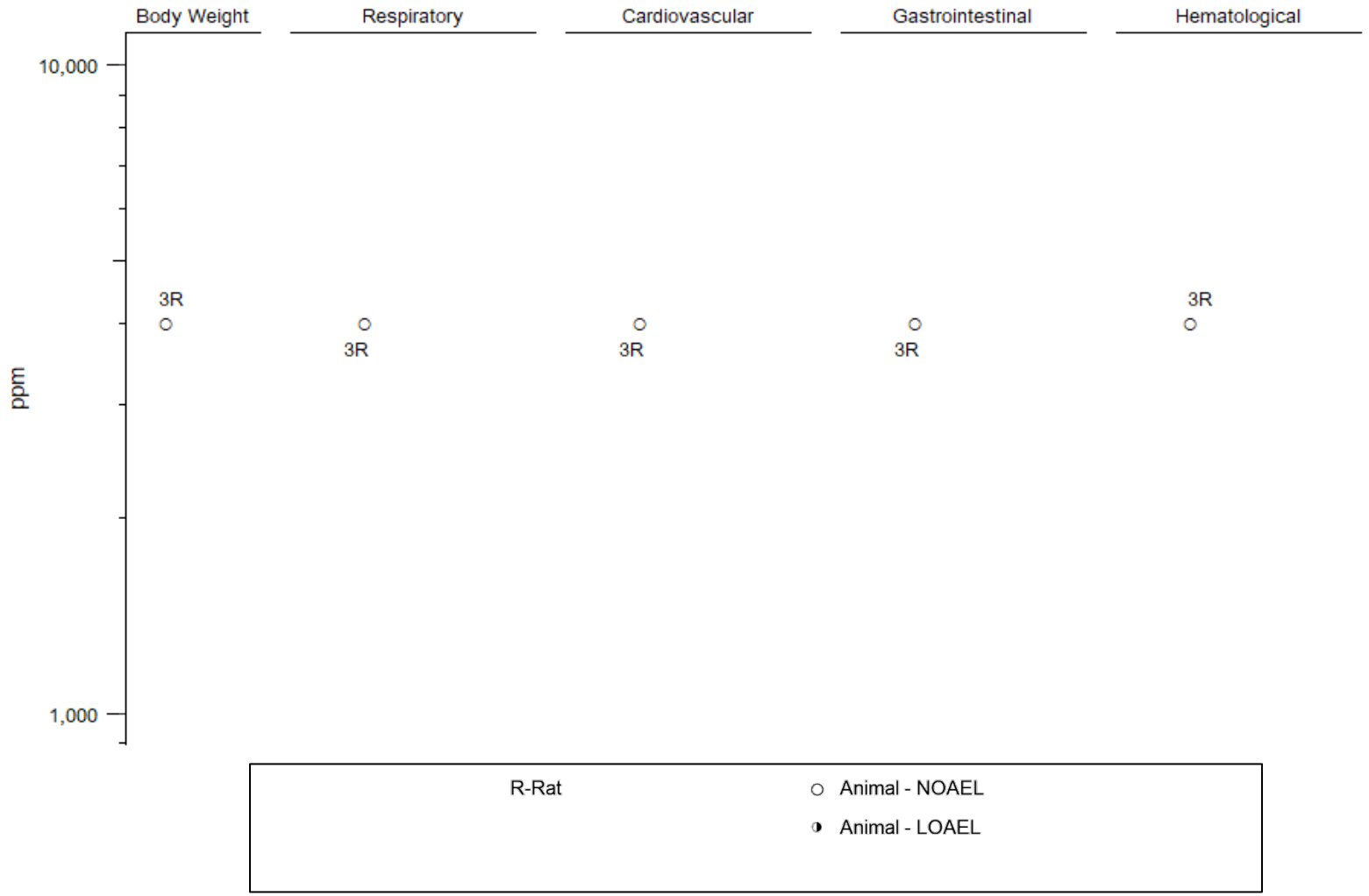


Figure 2-4. Levels of Significant Exposure to trans-1,2-Dichloroethene – Inhalation

Intermediate (15-364 days)

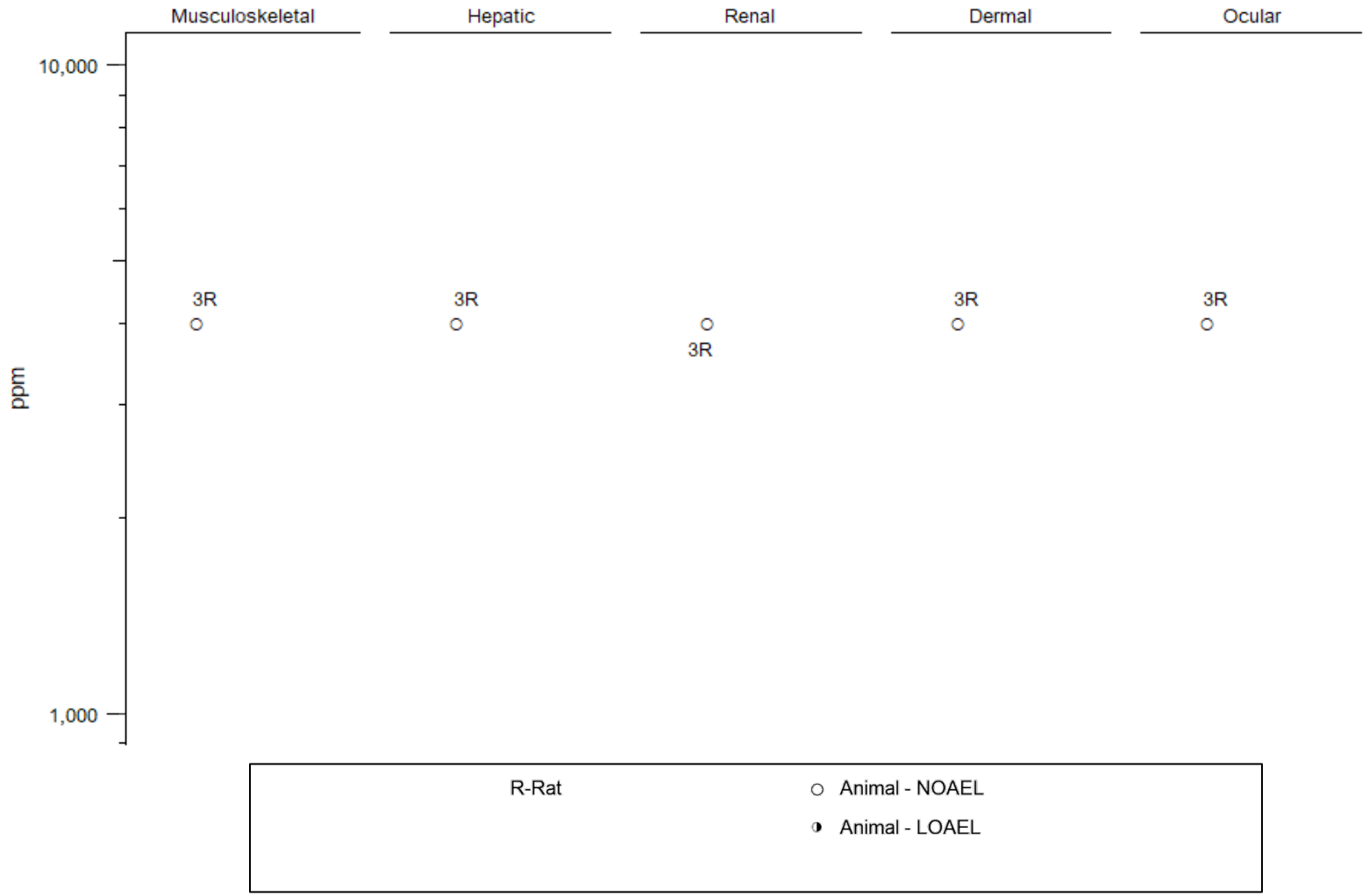


Figure 2-4. Levels of Significant Exposure to trans-1,2-Dichloroethene – Inhalation

Intermediate (15-364 days)

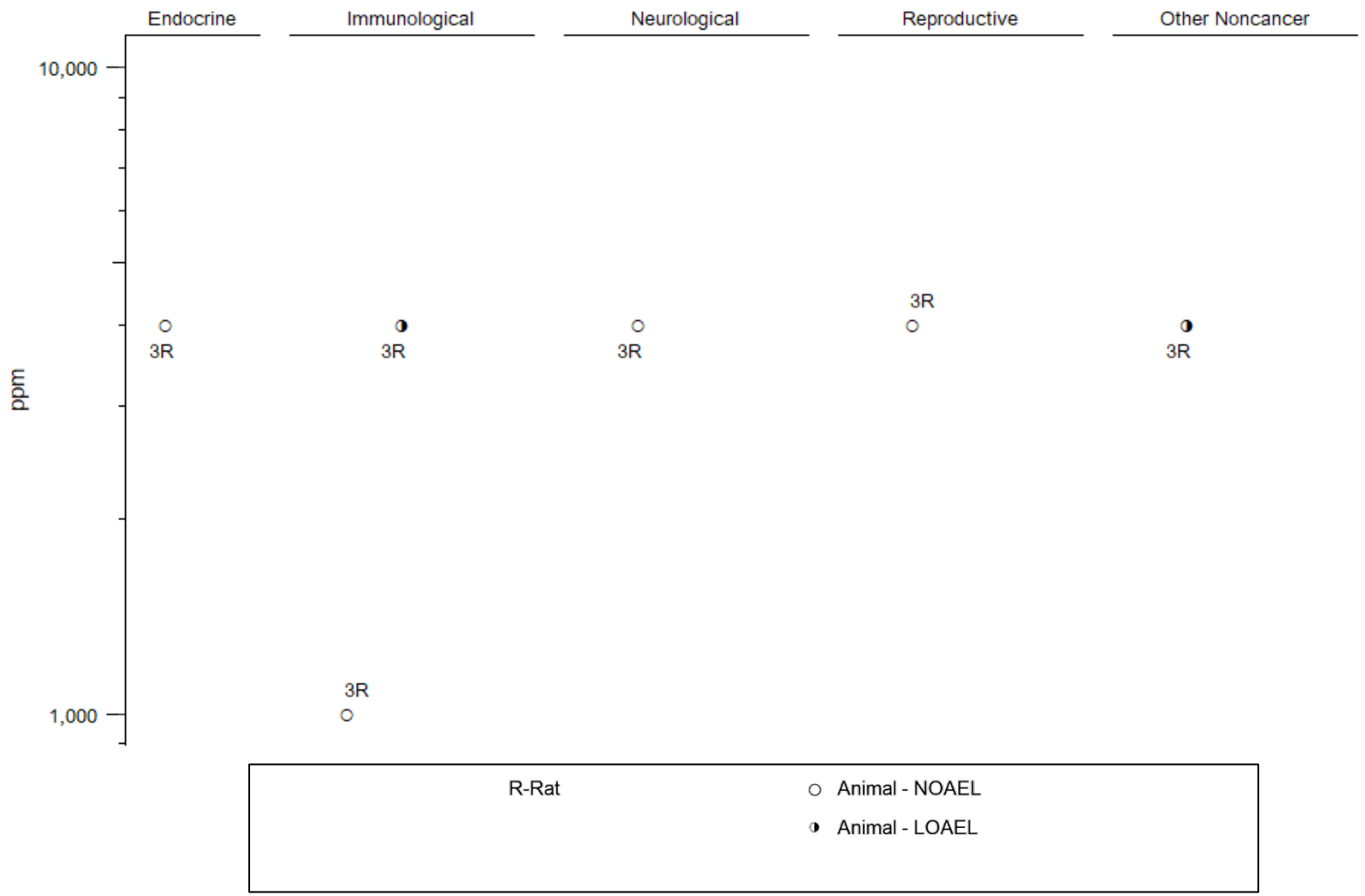


Table 2-2. Levels of Significant Exposure to trans-1,2-Dichloroethene – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
Freundt et al. 1977									
1	Rat (Wistar SPF) 10 F	Once (GO)	630, 940, 1,130, 1,300, 1,400, 1,600	GN, HP, LE	Death			1,130	LC_{50}
Hayes et al. 1987									
2	Rat (Sprague-Dawley) 10 M, 10 F	Once (GO)	NS	CS, GN, LE	Death			9,932 F 7,902 M	LD_{50}
NTP 2002									
3	Rat (Fischer-344) 10 M, 10 F	5 days (F)	M: 0, 344, 708, 1,437, 2,793, 5,591; F: 0, 307, 597, 1,227, 2,227, 4,500	BC, FI, HE	Hemato	4,500 F 5,591 M			
					Hepatic	4,500 F 5,591 M			
Barnes et al. 1985									
4	Mouse (CD-1) NS B	Once (G)	800, 1,200, 1,600, 2,000, 2,400, 3,000, 3,500	CS, GN, LE	Death			2,400 F 2,122 M	LD_{50}
Barnes et al. 1985									
5	Mouse (CD-1) 9–10 M	14 days 1 time/day (G)	0, 21, 210	BC, BW, GN, HE, OW	Bd wt	210			
					Resp	210			
					Hemato	21	210		Decreased fibrinogen levels (12%) and prothrombin time (7%)
					Hepatic	21			
					Renal	210			
					Immuno	210			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Munson et al. 1982									
6	Mouse (CD-1) NS B	Once (G)	NS	CS, GN, LE	Death			2,931 F 2,221 M	LD_{50}
Munson et al. 1982									
7	Mouse (CD-1) 10–12 M	Once/day 14 days (G)	0, 22, 220	BC, BW, GN, HE, IX, OW	Bd wt	220			
					Hemato	220			
					Hepatic	220			
					Immuno	220			
Shopp et al. 1985									
8	Mouse (CD-1) 9–10 M	14 days 1 time/day (G)	0, 21, 210	BC, IX	Immuno	210			
INTERMEDIATE EXPOSURE									
Hayes et al. 1987									
9	Rat (Sprague-Dawley) 20 M, 20 F	90 days *ad libitum* (W)	M: 0, 402, 1,314, 3,114 F: 0, 353, 1,257, 2,809	BC, CS, GN, HE, HP, LE, OW, UR, WI	Bd wt	2,809 F 3,114 M			
					Hemato	2,809 F 3,114 M			
					Hepatic	2,809 F 3,114 M			
					Renal	2,809 F 3,114 M			
					Repro	2,809 F 3,114 M			
					Other noncancer	2,809 F 3,114 M			Serum glucose (no change)

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
NTP 2002									
10	Rat (Fischer-344) 10 M, 10 F	14 weeks (F)	M: 0, 190, 380, 770, 1,540, 3,210; F: 0 190, 395, 780, 1,580, 3,245	BC, BW, CS, FI, GN, HE, HP, NX, OW, RX	Bd wt	3,245 F			
						3,210 M			
					Resp	3,245 F			
						3,210 M			
					Cardio	3,245 F			
						3,210 M			
					Gastro	3,245 F			
						3,120 M			
					Hemato	780 F	1,580 F		Decreased erythrocyte count
						190 M	380 M		
					Hepatic	3,245 F			
						3,120 M			
					Renal	3,245 F			
						3,120 M			
					Dermal	3,245 F			
						3,120 M			
					Endocr	3,245 F			
						3,120 M			
					Immuno	3,245 F			
						3,120 M			
					Neuro	3,245 F			
						3,120 M			
					Repro	3,245 F			
						3,120 M			
					Other noncancer	3,245 F			
						3,210 M			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Barnes et al. 1985									
11	Mouse (CD-1) 140–260 M, 140–260 F	90 days *ad libitum* (W)	M: 0, 17, 175, 387 F: 0, 23, 224, 452	BC, BI, GN, HE, OW, WI	Bd wt	452 F			
						387 M			
					Hepatic	452 F			
						387 M			
					Renal	452 F			
						387 M			
					Immuno	452 F			
						387 M			
					Other noncancer		23 F 17 M		Serum glucose increased by 28% in females and 27% in males
NTP 2002									
12	Mouse (B6C3F1) 10 M, 10 F	14 weeks (F)	M: 0, 480, 920, 1,900, 3,850, 8,065; F: 0, 450, 915, 1,830, 3,760, 7,925	BW, CS, FI, GN, HP, NX, OW, RX	Bd wt	7,925 F 3,760 M	8,065 M		Terminal body weight decreased by 10.7%
					Resp	7,925 F			
						8,065 M			
					Cardio	7,925 F			
						8,065 M			
					Gastro	7,925 F			
						8,065 M			
					Hepatic	7,925 F			
						8,065 M			
					Renal	7,925 F			
						8,065 M			
					Dermal	7,925 F			
						8,065 M			
					Endocr	7,925 F			
						8,065 M			
					Immuno	7,925 F			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
						8,065 M			
					Neuro	7,925 F			
						8,065 M			
					Repro	7,925 F			
						8,065 M			
Shopp et al. 1985									
13	Mouse (CD-1) 6–23 B	90 days *ad libitum* (W)	M: 0, 17, 175, 387 F: 0, 23, 224, 452	IX, OW	Immuno	452 F 17 M	175 M[b]		Decreased humoral immunity (reduction in splenic AFCs against SRBCs) ($BMDL_{1SD}$=16.75)

[a]The number corresponds to entries in Figure 2-5.
[b]Used to derive a provisional intermediate-duration oral MRL. Using BMD modeling, BMD_{10} and $BMDL_{1SD}$ values of 77.27 and 16.75 mg/kg/day, respectively, were calculated for humoral immune suppression. The $BMDL_{1SD}$ was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability), resulting in a provisional acute-duration MRL of 0.2 mg/kg/day for trans-1,2-dichloroethene. See Appendix A for more detailed information regarding the provisional MRL.

AFC = antibody-forming cell; B = both males and females; BC = blood chemistry; Bd wt or BW = body weight; BMD = benchmark dose; BMDL = lower 95% confidence limit on the benchmark dose; BI = biochemical changes; Cardio = cardiological; CS = clinical signs; Endocr = endocrine; (F) = feed; F = female(s); FI = food intake; (G) = gavage; (GO) = gavage in oil; Gastro = gastrointestinal; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; IX = immunotoxicity; LD_{50} = median lethal dose; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); MRL = Minimal Risk Level; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; NX = neurotoxicity; OW = organ weight; Repro = reproductive; Resp = respiratory; RX = reproductive toxicity; SD = standard deviation; SRBCs = sheep red blood cells; UR = urinalysis; (W) = water; WI = water intake

Figure 2-5. Levels of Significant Exposure to trans-1,2-Dichloroethene – Oral

Acute (≤14 days)

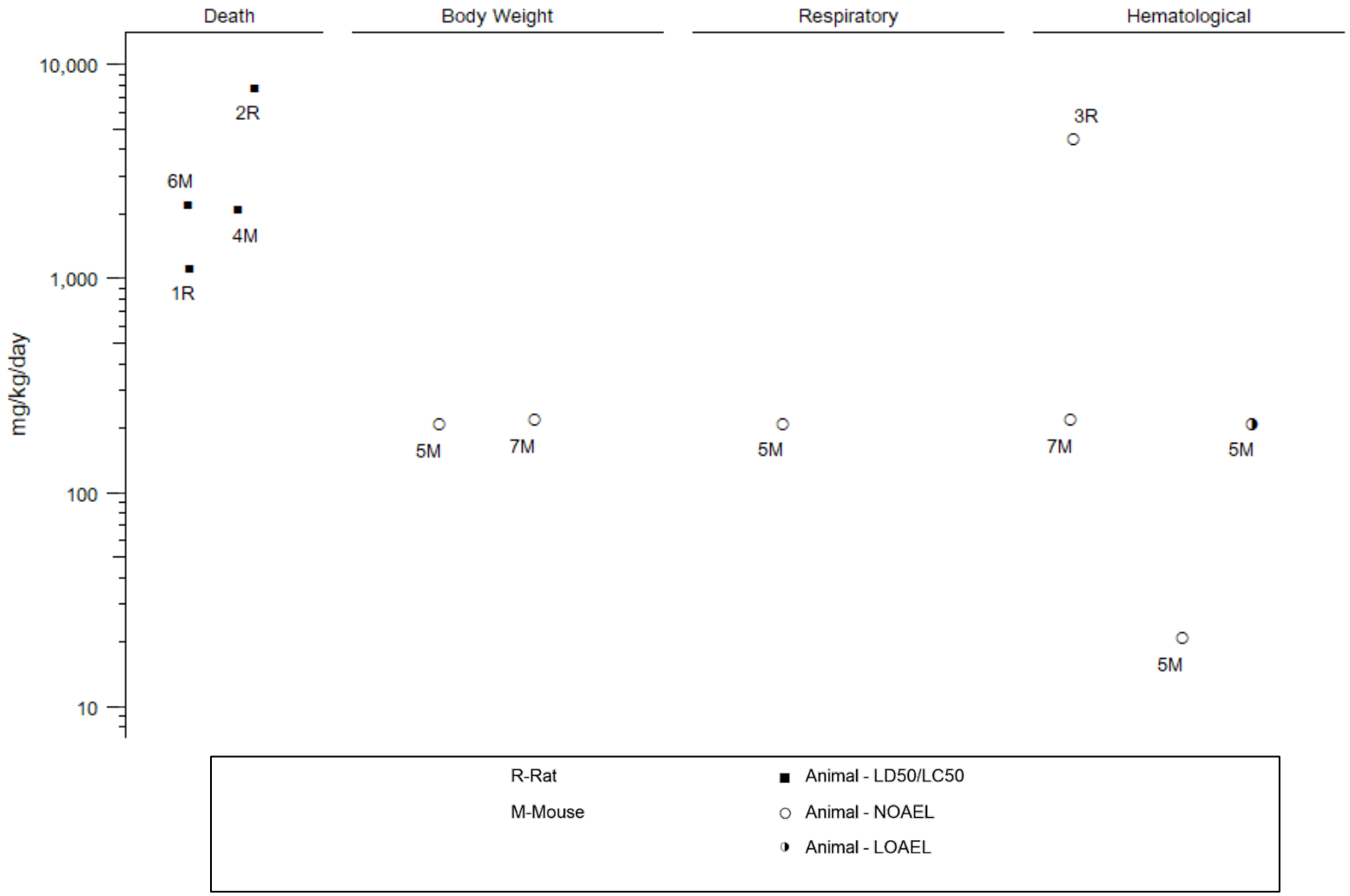


Figure 2-5. Levels of Significant Exposure to trans-1,2-Dichloroethene – Oral

Acute (≤14 days)

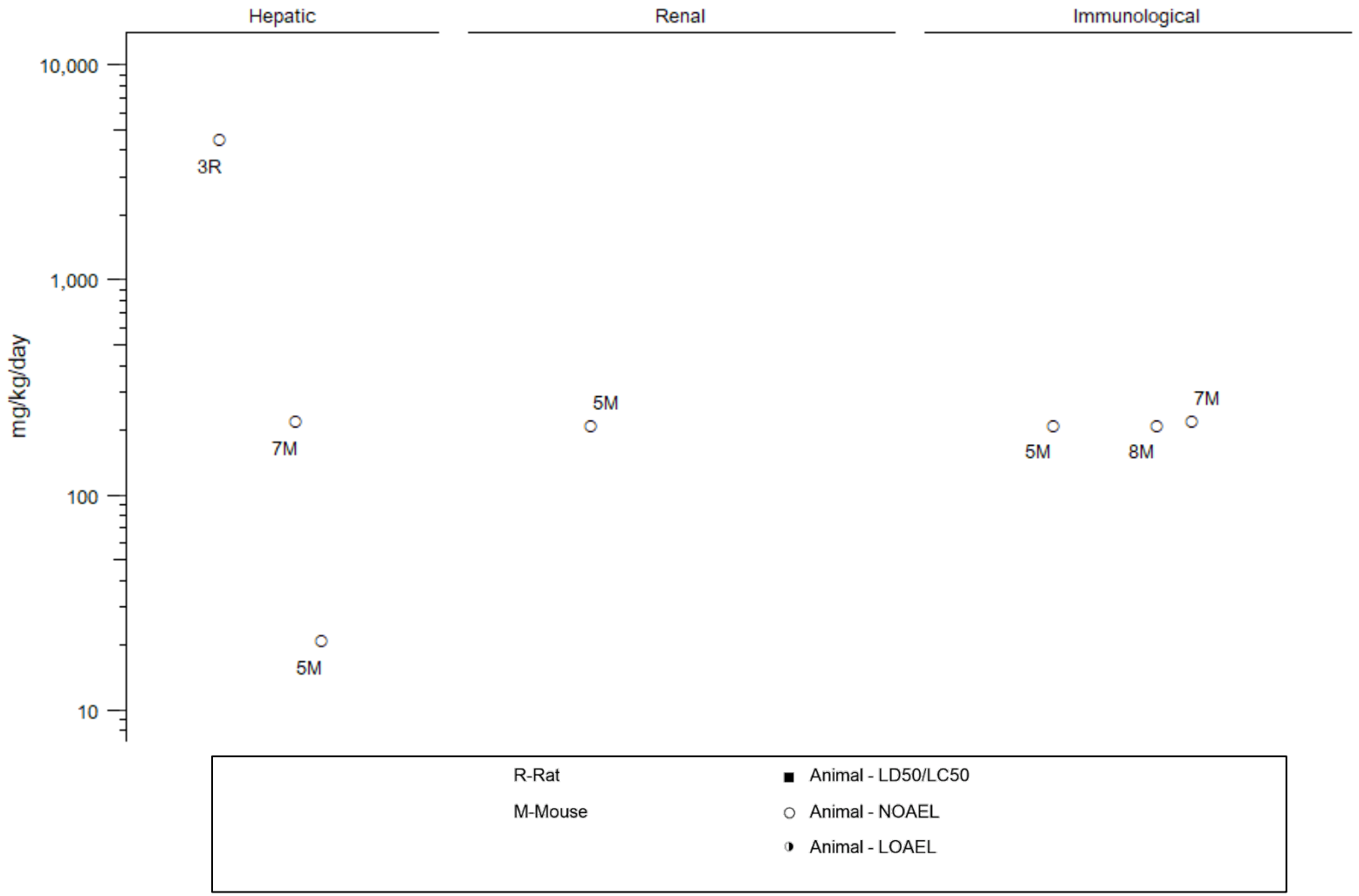


Figure 2-5. Levels of Significant Exposure to trans-1,2-Dichloroethene – Oral

Intermediate (15-364 days)

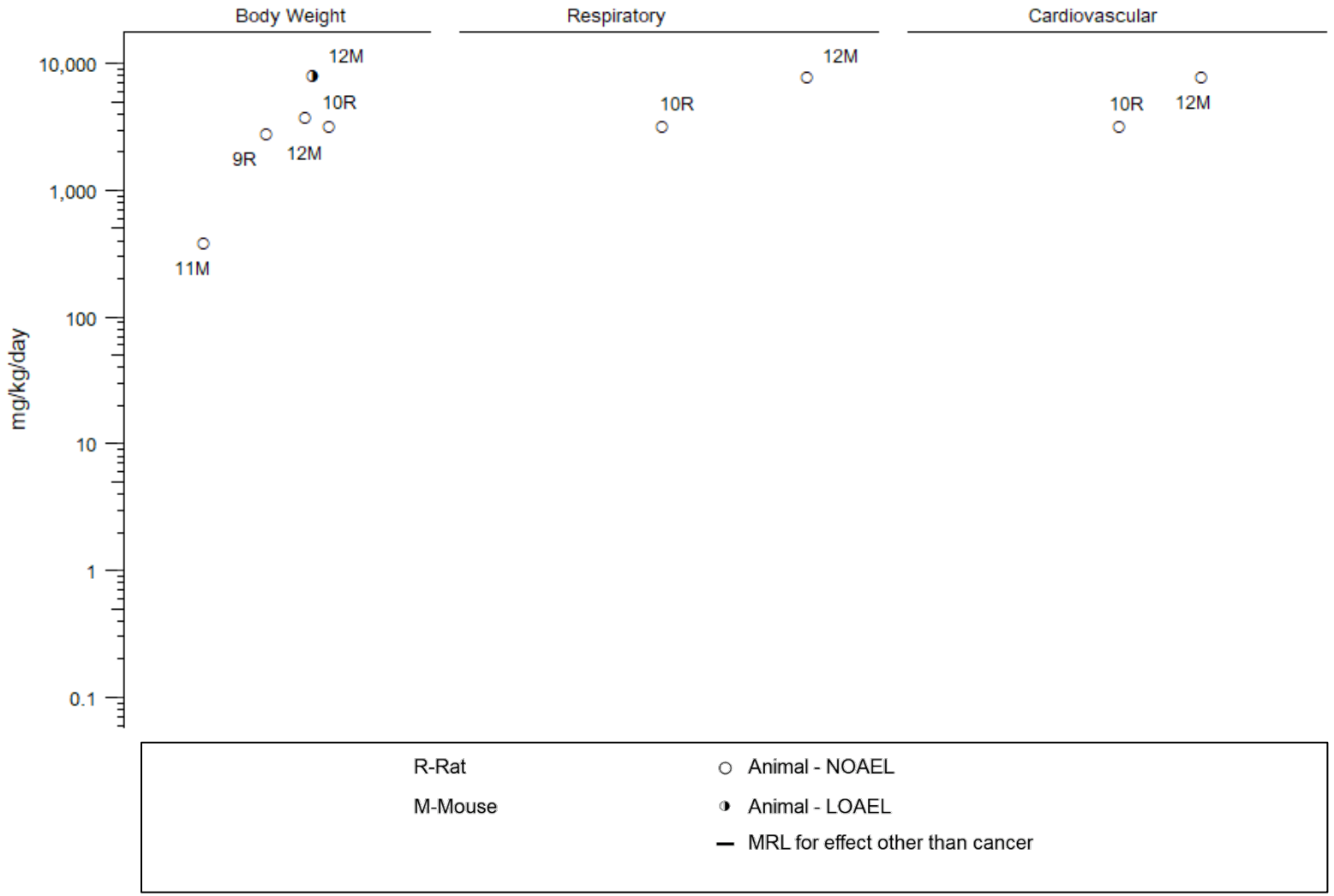


Figure 2-5. Levels of Significant Exposure to trans-1,2-Dichloroethene – Oral

Intermediate (15-364 days)

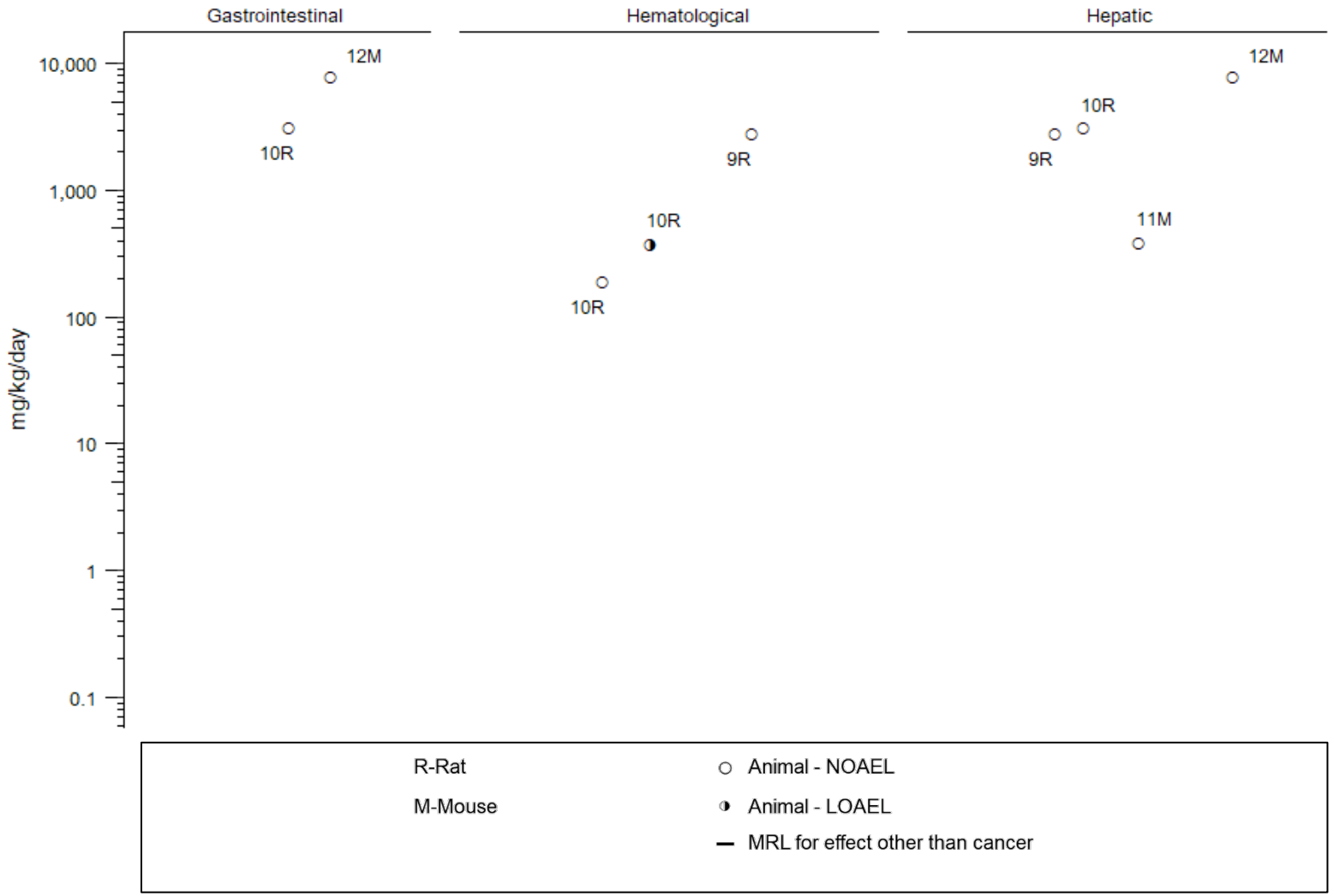


Figure 2-5. Levels of Significant Exposure to trans-1,2-Dichloroethene – Oral

Intermediate (15-364 days)

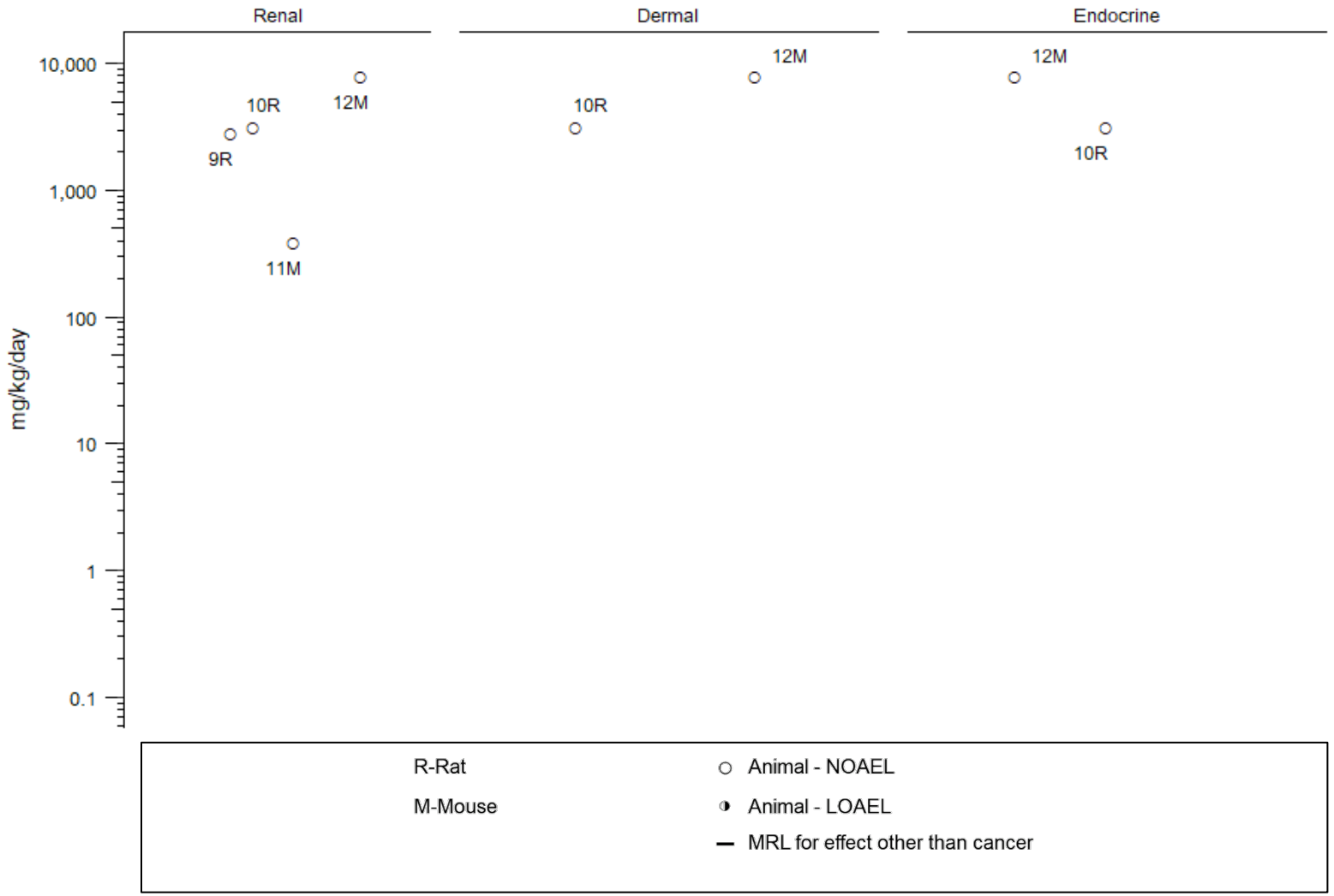


Figure 2-5. Levels of Significant Exposure to trans-1,2-Dichloroethene – Oral
Intermediate (15-364 days)

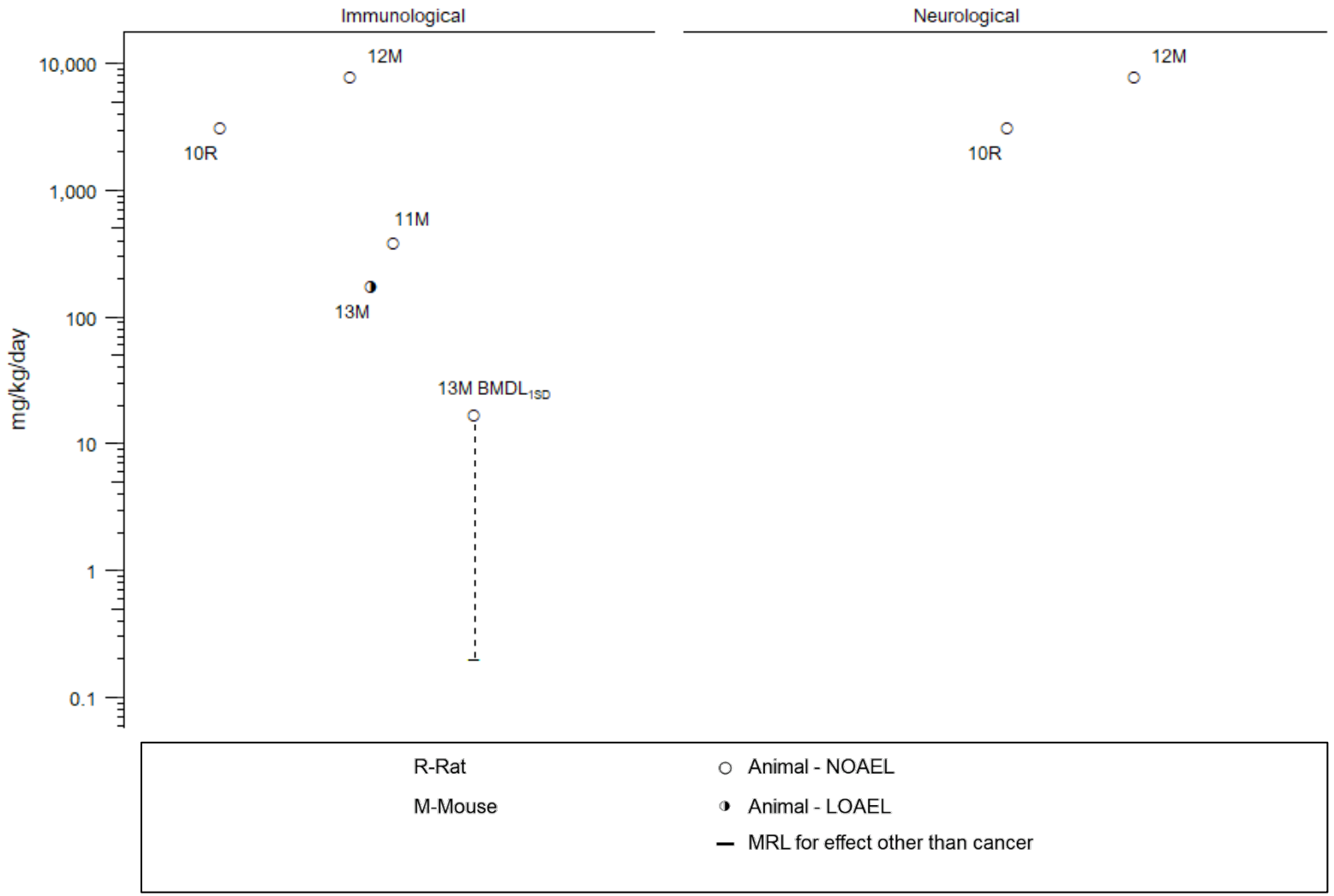


Figure 2-5. Levels of Significant Exposure to trans-1,2-Dichloroethene – Oral
Intermediate (15-364 days)

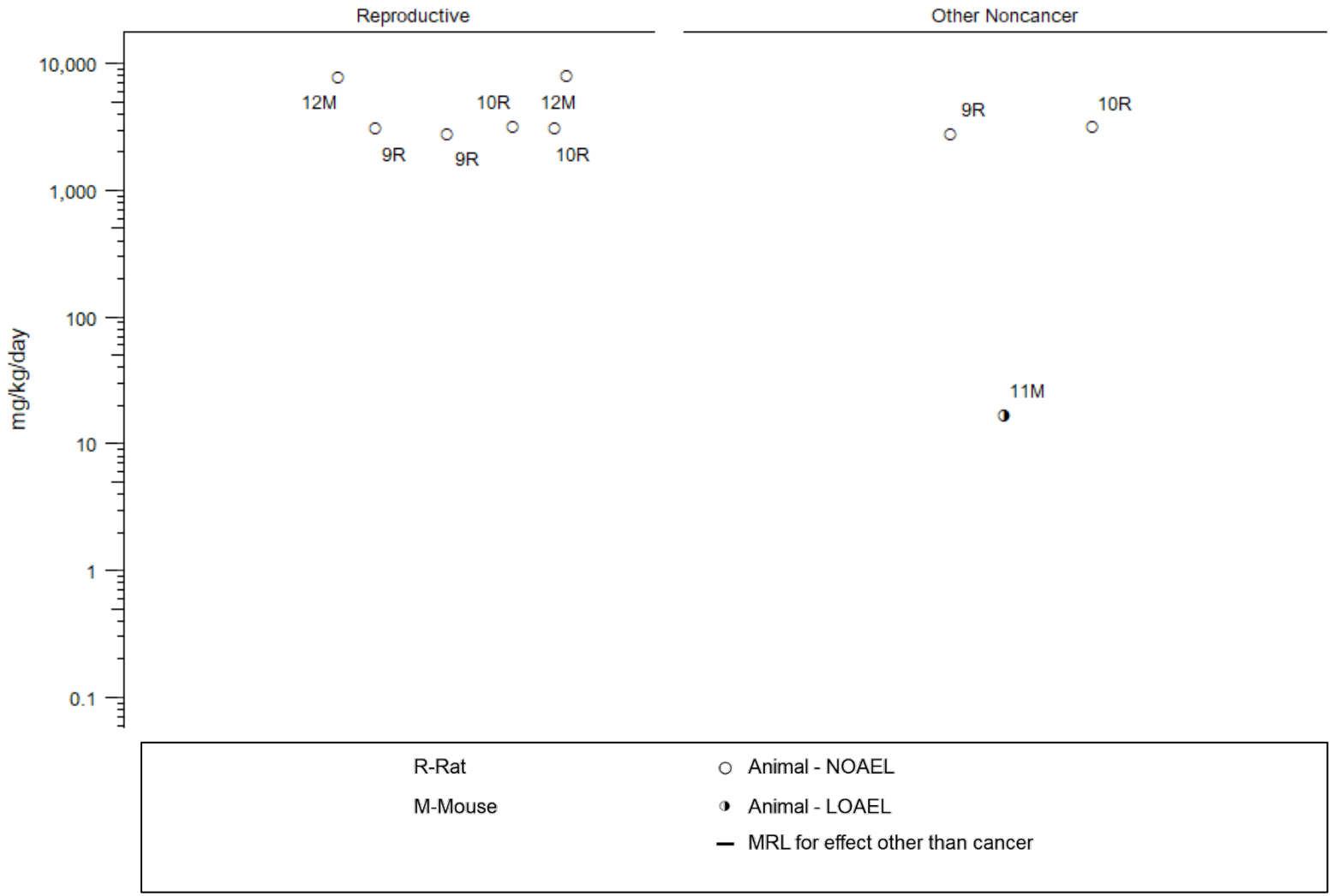


Table 2-3. Levels of Significant Exposure to trans-1,2-Dichloroethene – Dermal

Figure key	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
Brock 1990									
	Rabbit (NS) 5 M, 1 F	24 hours	170 mg/kg	CS	Dermal		170		Mild-to-moderate erythema
Brock 1990									
	Rabbit (NS) 2 M, 3 F	24 hours	5,000 mg/kg	BW, CS, LE	Bd wt		5,000		Body weight loss (magnitude not reported)
					Dermal			5,000	Severe dermal irritation
DuPont 1988a									
	Rabbit (New Zealand) 2M, 2F	24 hours	5,000 mg/kg	BW, CS, LE	Dermal			5,000	Dermal irritation, erythema, edema, necrosis, fissuring of the skin, epidermal scaling
DuPont 1988b									
	Rabbit (New Zealand) 5 M, 1 F	48 hours	630 mg/kg	CS	Dermal		630		Mild-to-moderate erythema
DuPont 1988c									
	Rabbit (New Zealand White) 2 F	20 seconds (eyes)	0.01 mL	CS	Ocular			0.01 mL	Transient severe corneal opacity, moderate iritis, and conjunctivitis

Bd wt or BW = body weight; CS = clinical signs; F = female(s); LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); NOAEL = no-observed-adverse-effect level

Table 2-4. Levels of Significant Exposure to cis-1,2-Dichloroethene – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
McCauley et al. 1990, 1995									
1	Rat (Sprague-Dawley) 10 M, 10 F	14 days 1 time/day (GO)	0, 97, 290, 970, 1,900	BW, BC, CS, FI, HE, HP, OW, WI	Bd wt	1,900			
					Resp	1,900			
					Cardio	1,900			
					Gastro	1,900			
					Hemato	97 F	290 F		Decreased hematocrit
						1,900 M			
					Musc/skel	1,900			
					Hepatic	970 F	1,900 F		Increased serum cholesterol
						1,900 M			
					Renal	1,900			
					Dermal	1,900			
					Endocr	1,900			
					Immuno	1,900			
					Repro	1,900			
INTERMEDIATE EXPOSURE									
McCauley et al. 1990, 1995									
2	Rat (Sprague-Dawley) 10 M, 10 F	90 days 1 time/day (GO)	0, 32, 97, 290, 870	BC, BW, FI, GN, HE, HP, OW, WI	Bd wt	870 F 290 M		870 M	Body weight gain decreased by 37%
					Resp	870			
					Cardio	870			
					Gastro	870			
					Hemato	97 F	290 F		Decreased hematocrit
						32 M	97 M		Decreased hematocrit
					Musc/skel	870			
					Hepatic	870			
					Renal	870			
					Dermal	870			

Table 2-4. Levels of Significant Exposure to cis-1,2-Dichloroethene – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Endocr	870			
					Immuno	870			
					Neuro	870			
					Repro	870			

[a]The number corresponds to entries in Figure 2-6.

BC = blood chemistry; Bd wt or BW = body weight; Cardio = cardiological; CS = clinical signs; Endocr = endocrine; F = female(s); FI = food intake; (GO) = gavage in oil; Gastro = gastrointestinal; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; LOAEL = lowest-observed-adverse-effect level; M = male(s); Musc/skel = musculoskeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; OW = organ weight; Repro = reproductive; Resp = respiratory; WI = water intake

Figure 2-6. Levels of Significant Exposure to cis-1,2-Dichloroethene – Oral

Acute (≤14 days)

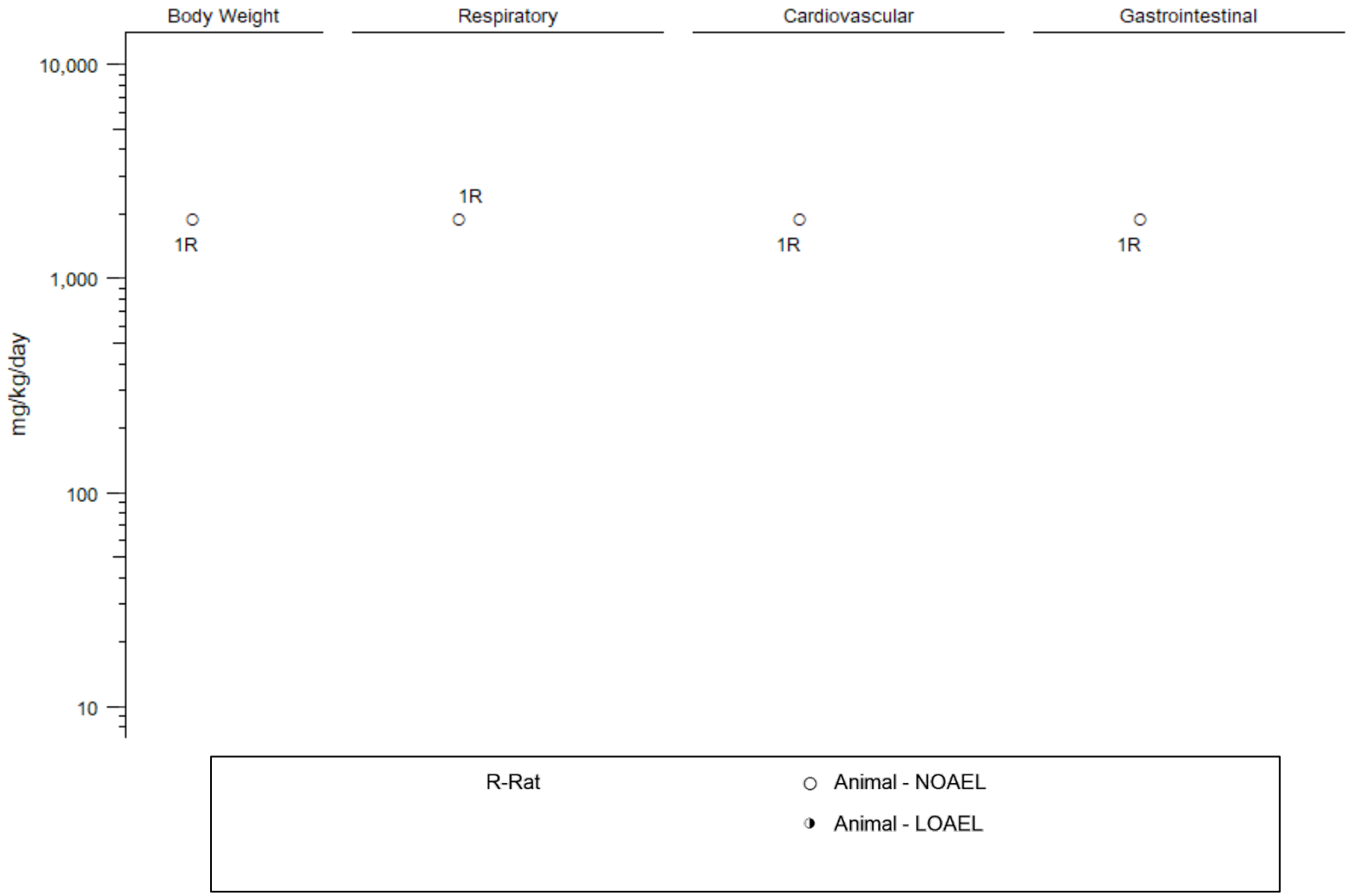


Figure 2-6. Levels of Significant Exposure to cis-1,2-Dichloroethene – Oral

Acute (≤14 days)

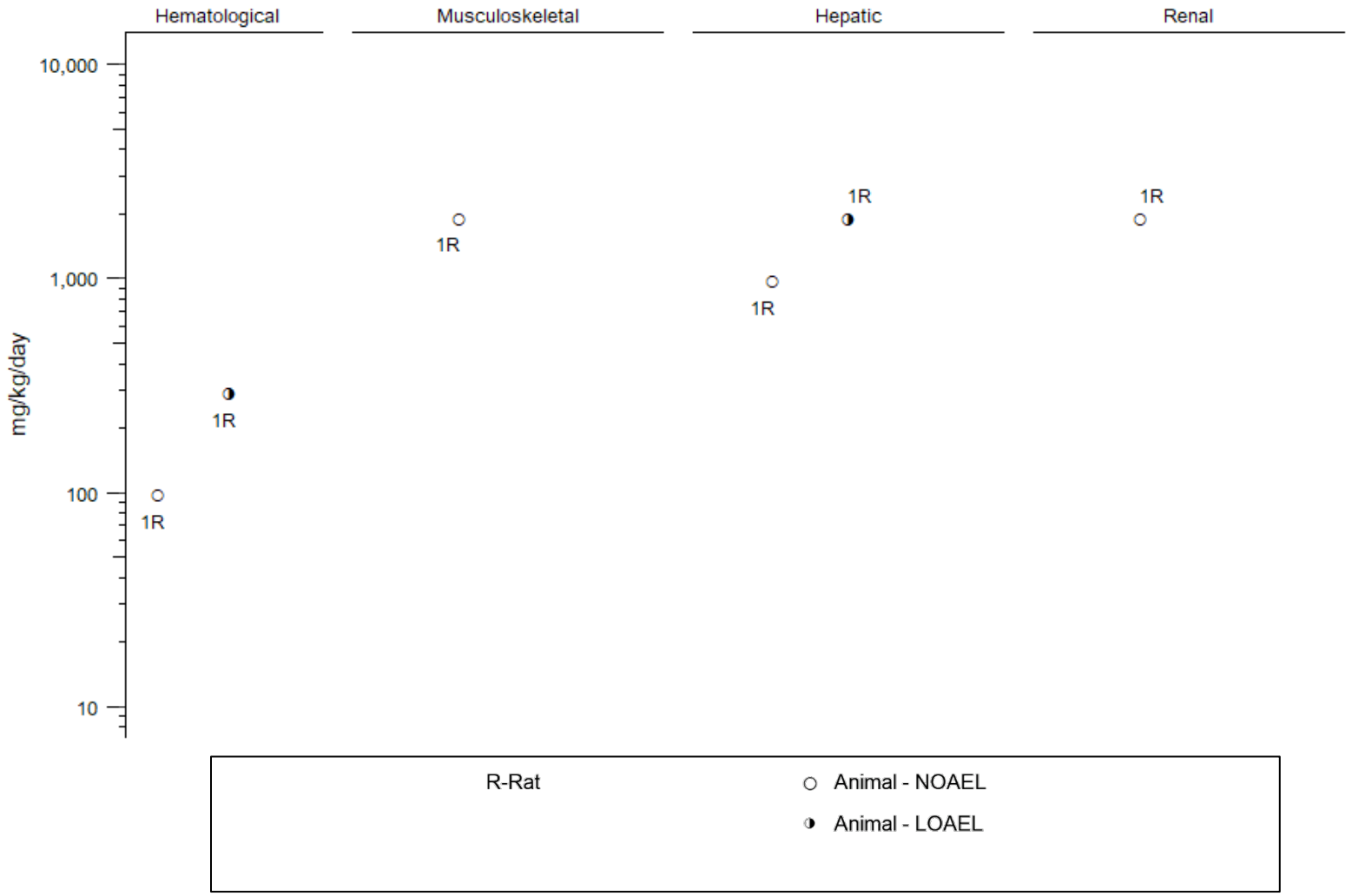


Figure 2-6. Levels of Significant Exposure to cis-1,2-Dichloroethene – Oral

Acute (≤14 days)

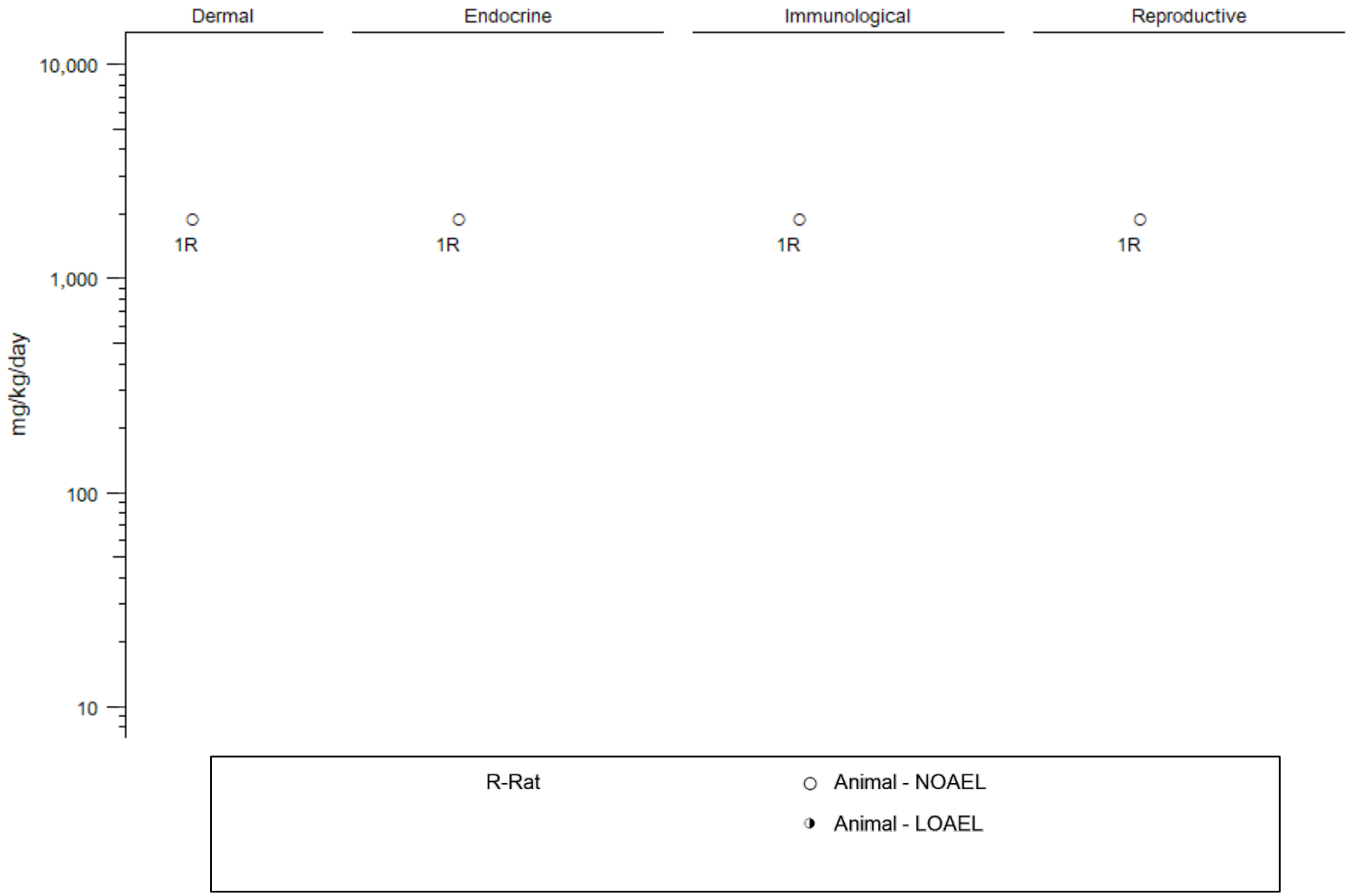


Figure 2-6. Levels of Significant Exposure to cis-1,2-Dichloroethene – Oral
Intermediate (15-364 days)

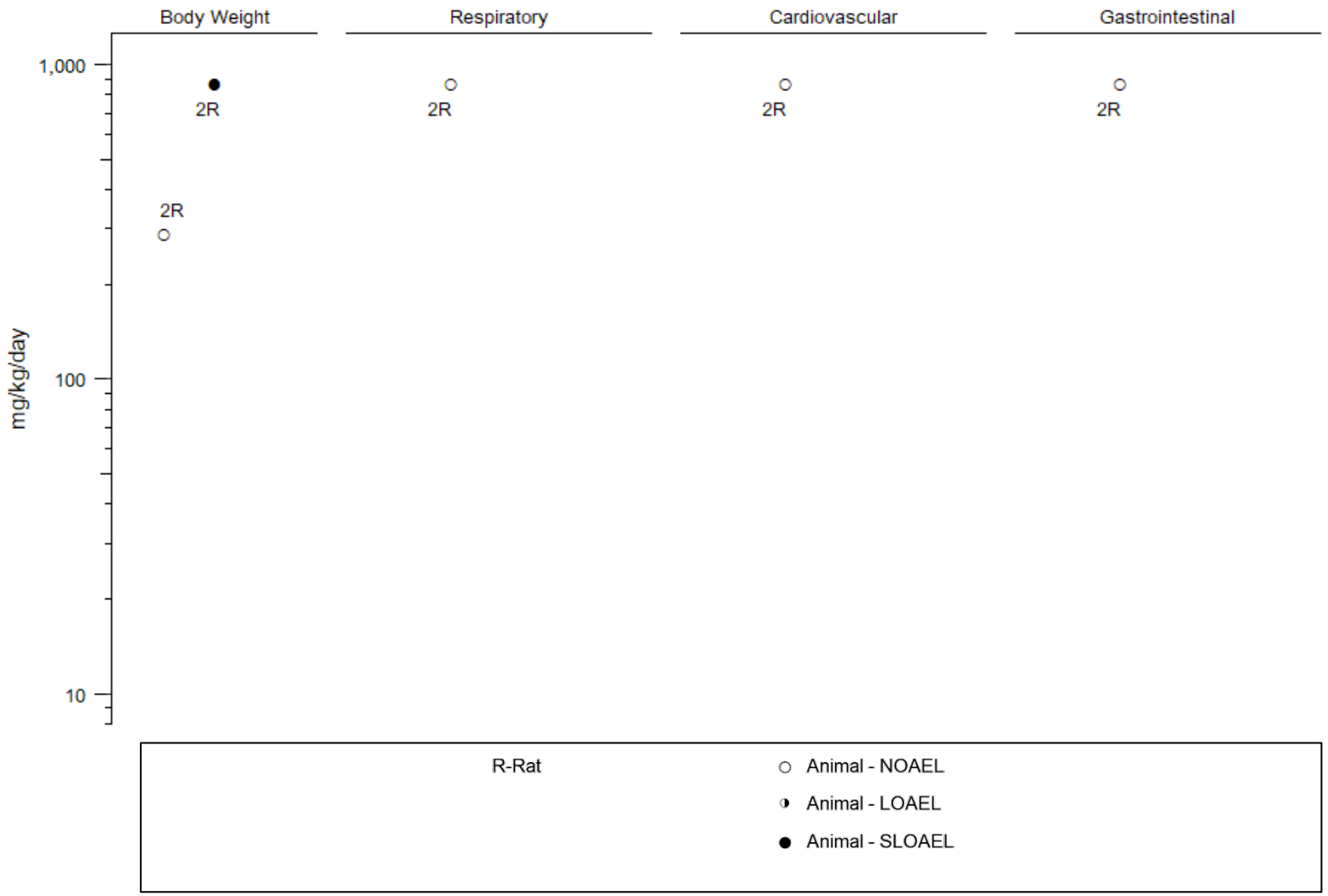


Figure 2-6. Levels of Significant Exposure to cis-1,2-Dichloroethene – Oral

Intermediate (15-364 days)

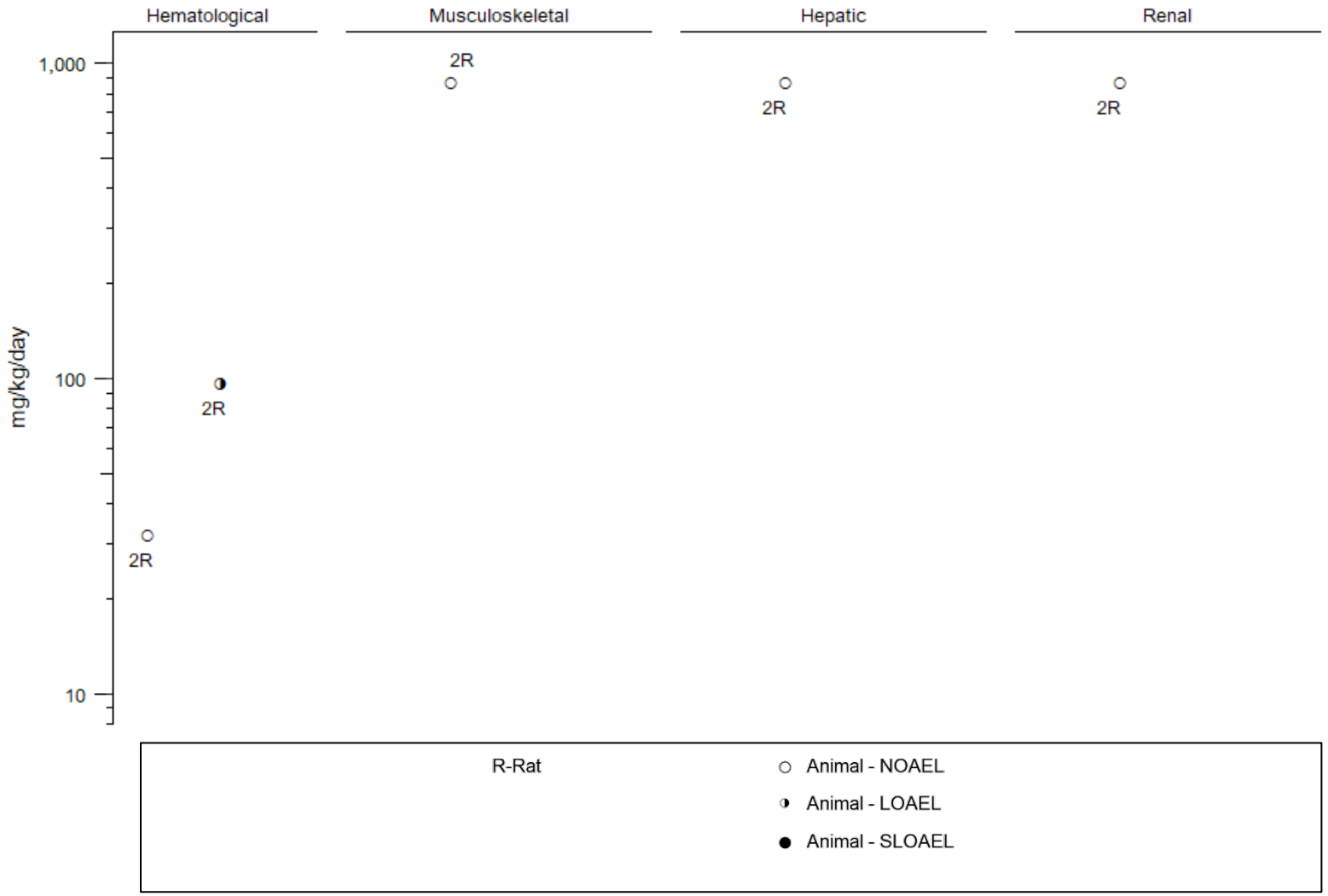


Figure 2-6. Levels of Significant Exposure to cis-1,2-Dichloroethene – Oral

Intermediate (15-364 days)

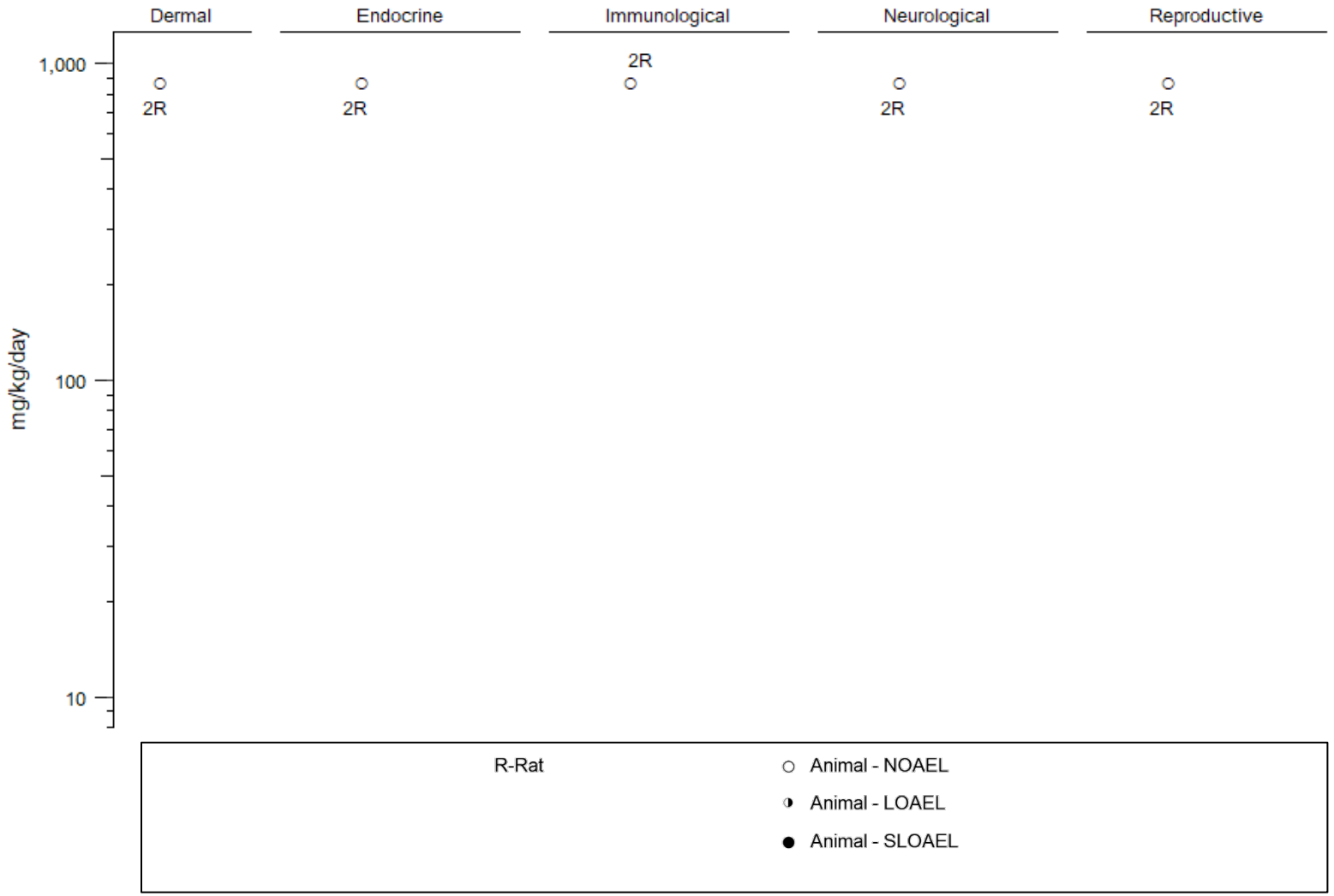


Table 2-5. Levels of Significant Exposure to Mixtures of cis- and trans-1,2-Dichloroethene – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
Dow Chemical Company 1960									
1	Rat (NS) 9 M	Once 0.1, 0.2, or 0.35 hours	50,123	CS, LE	Death			50,123	100% lethality after 19 minutes of exposure
					Neuro			50,123	Tremors during exposure for 0.1 and 0.2 hours
Dow Chemical Company 1960									
2	Rat (NS) 9 M	Once 0.2, 0.5, or 1.5 hours	29,035	CS, LE	Death			29,035	100% lethality in rats exposed for 1.5 hours
					Neuro			29,035	Unconsciousness and tremors for all exposure durations
Dow Chemical Company 1960									
3	Rat (NS) 9 M	Once 4 or 7 hours	16,810	CS, LE	Death			16,810	Death in 6/9 rats exposed for 4 and 7 hours
					Neuro			16,810	Tremors and prone position in rats exposed for 7 hours
Dow Chemical Company 1960									
4	Rat (NS) 9 M	Once 1 hour	14,814	CS, LE					
Dow Chemical Company 1960									
5	Rat (NS) 9 M	Once 2, 4, or 7 hours	7,297	CS, LE	Neuro			7,297	Tremors and staggering in rats exposed for 7 hours
Dow Chemical Company 1994									
6	Rat (NS) 10 M, 10 F	7 hours/day 5 days/week 2 weeks	1,000	BC, BW, CS, HE, LE, OW	Bd wt	1,000			
					Hemato	1,000			
					Hepatic	1,000			
					Renal	1,000			

Table 2-5. Levels of Significant Exposure to Mixtures of cis- and trans-1,2-Dichloroethene – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Dow Chemical Company 1994									
7	Rabbit (NS) 3M, 3F	7 hours/day 5 days/week 2 weeks	1,000	BC, BW, CS, HE, LE, OW	Bd wt	1,000			
					Hemato	1,000			
					Hepatic	1,000			
					Renal	1,000			
INTERMEDIATE EXPOSURE									
Dow Chemical Company 1994									
8	Rat (NS) 12 M, 12 F	7 hours/day 5 days/week 6 months	0, 500, 1,000	BC, BW, CS, HE, LE, OW	Bd wt	1,000			
					Hemato	1,000			
					Hepatic	1,000			
					Renal	1,000			
Dow Chemical Company 1994									
9	Rabbit (NS) 3 M, 3 F	7 hours/day 5 days/week 6 months	0, 500, 1,000	BC, BW, CS, HE, LE, OW	Bd wt	1,000			
					Hemato	1,000			
					Hepatic	1,000			
					Renal	1,000			

[a]The number corresponds to entries in Figure 2-7.

BC = blood chemistry; Bd wt or BW = body weight; CS = clinical signs; F = female(s); HE = hematology; Hemato = hematological; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OW = organ weight

Figure 2-7. Levels of Significant Exposure to Mixtures of cis- and trans-1,2-Dichloroethene – Inhalation

Acute (≤14 days)

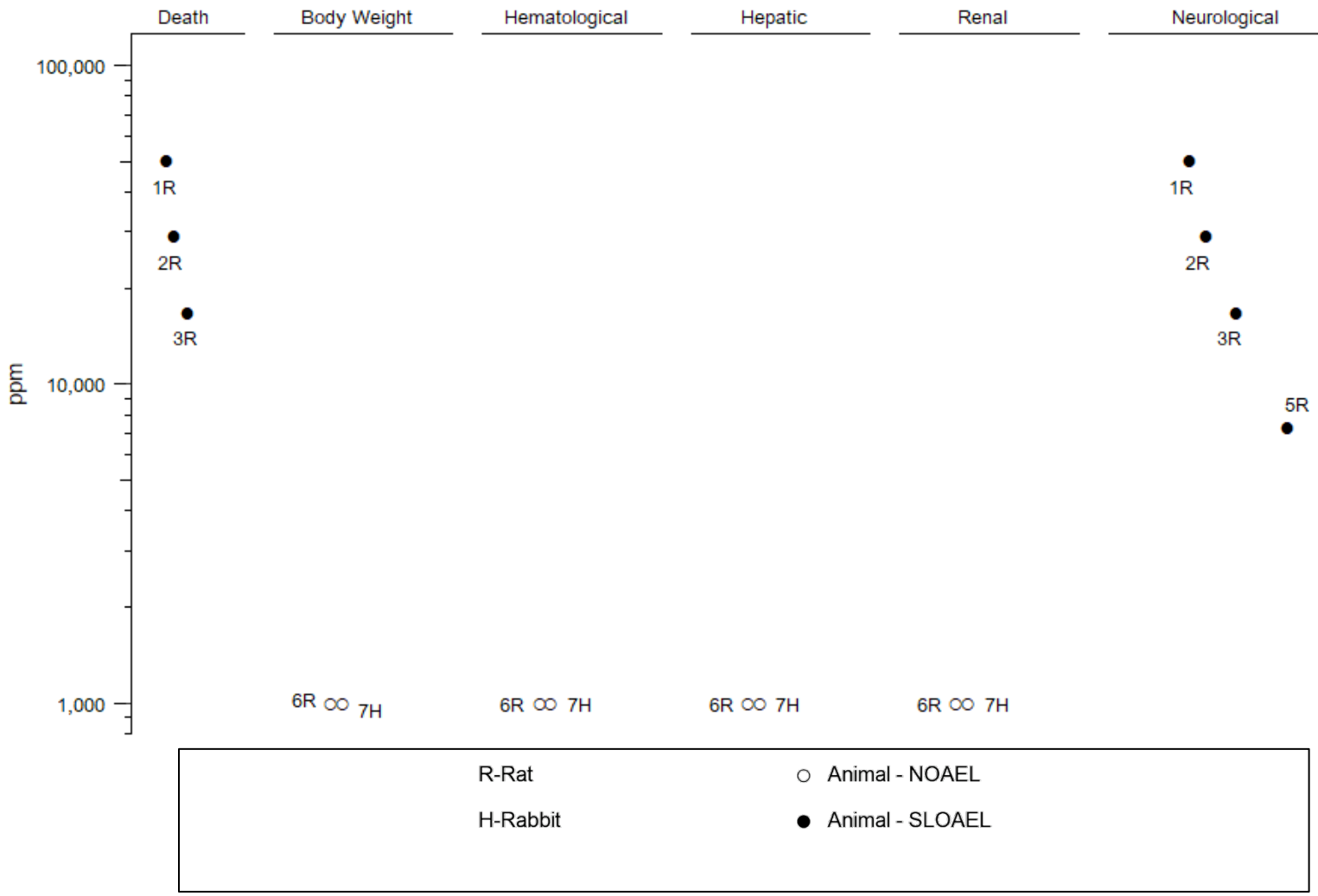
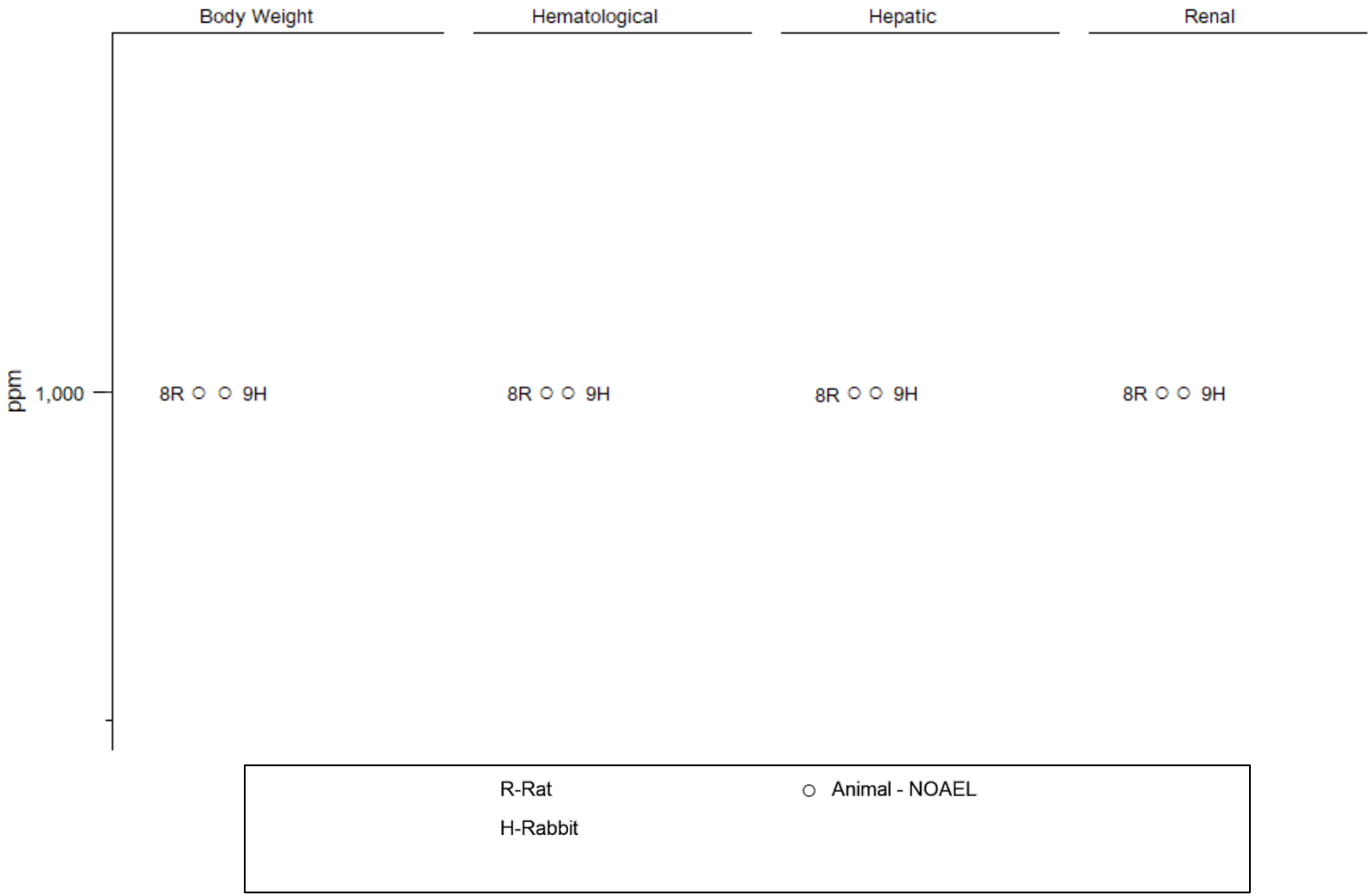


Figure 2-7. Levels of Significant Exposure to Mixtures of cis- and trans-1,2-Dichloroethene – Inhalation

Intermediate (15-364 days)



2.2 DEATH

trans-1,2-Dichloroethene. No studies were located regarding lethality in humans from inhalation, oral, or dermal exposure to trans-1,2-dichloroethene. In laboratory animals, acute- and intermediate-duration studies have evaluated lethality of trans-1,2-dichloroethene by inhalation, oral, and dermal exposure. Inhalation studies show that lethality occurs at high exposure levels. In mice, a 6-hour LC_{50} value of 21,723 ppm was determined; the cause of death was not reported (Gradiski et al. 1978). No maternal mortality was observed in rats in a gestational exposure study of inhaled trans-1,2-dichloroethene at the highest concentrations tested of 12,000 ppm (Hurtt et al. 1993). In a 90-day inhalation study in rats, no treatment-related deaths occurred at concentrations up to 4,000 ppm, the highest concentration tested (DuPont 1998). For oral exposure, an of LD_{50} value of 9.932 mg/kg was determined in rats (Hayes et al. 1987) and the range of LD_{50} values in mice was 2,211–2,931 mg/kg (Barnes et al. 1985; Munson et al. 1982). The cause of death was not reported; however, neurological symptoms associated with lethal oral doses included decreased activity, ataxia, suppressed or total loss of righting reflex, and depressed respiration (Barnes et al. 1985; Hayes et al. 1987). No treatment-related deaths were observed in intermediate-duration oral studies in rats and mice. The highest doses of trans-1,2-dichloroethene tested in these studies were as follows: 3,114 mg/kg/day in male rats and 2,809 mg/kg/day in female rats in a 90-day drinking water study (Hayes et al. 1987); 3,210 and 3,245 mg/kg/day in male and female rats, respectively, in a 14-week dietary exposure study (NTP 2002); and 8,065 and 7,925 mg/kg/day in male and female mice, respectively, in a 14-week dietary exposure study (NTP 2002). Dermal exposure studies in rabbits did not observe any lethality following a 24-hour exposure to 5,000 mg/kg trans-1,2-dichloroethene (Brock 1990; DuPont 1988a).

cis-1,2-Dichloroethene. No studies were located regarding lethality in humans from inhalation, oral, or dermal exposure to cis-1,2-dichloroethene, and few studies have evaluated lethality in laboratory animals. Mortality exhibited dose-dependence, with no deaths at 12,000 ppm, 4/10 deaths at 13,500 ppm, and 100% mortality at 15,700 and 23,200 ppm. The cause of death was not specifically reported, although neurological effects (unresponsive to stimuli) were reported. No additional studies evaluating lethality of inhaled cis-1,2-dichloroethene were identified. A 14-day gavage study in rats did not observe any treatment-related lethality. The study authors stated that deaths in the two highest dose groups (970 mg/kg/day: 2/20 deaths; 1,900 mg/kg/day: 5/20 deaths) were due to gavage errors, although no deaths were observed in lower dose groups (≤290 mg/kg/day). In a 90-day gavage study in rats, no treatment-related mortality was observed at doses up to 870 mg/kg/day, the highest dose tested

(McCauley et al. 1990, 1995). No studies evaluating mortality following dermal exposure to cis-1,2-dichloroethene were identified.

Mixed Isomers or Isomeric Composition Not Reported. In humans, a single fatality was reported after inhalation of 1,2-dichloroethene vapor in a small enclosure (Hamilton 1934). No information regarding level or duration of exposure or isomeric composition of the vapor was reported. No additional information regarding lethal effects in humans following inhalation of 1,2-dichloroethene was identified.

Information on lethality of mixed cis- and trans-1,2-dichloroethene in laboratory animals is available for acute- and intermediate-duration inhalation exposures and acute-duration oral exposure. A series of single exposure inhalation studies in rats examined lethality of a mixture of trans- and cis-1,2-dichloroethene; the percentage of each isomer in the mixture was not reported (Dow Chemical Company 1960). Lethality was 100% in rats exposed to 50,123 ppm for 19 minutes and 29,035 ppm for 1.5 hours. Results of this study show that lethality of the mixed isomer exposure exhibited dose-dependence. For example, no lethality was observed in rats exposed to 7,297 ppm for 4 or 7 hours, compared to mortality in 6/9 rats exposed to 16,810 ppm for 4 or 7 hours. The cause of death was not reported, although signs of neurotoxicity were observed. No mortality was observed in rats or rabbits exposed to 1,000 ppm of a mixture of 58% cis- and 42% trans-1,2-dichloroethene for 2 weeks (Dow Chemical Company 1994). In a 6-month inhalation study of a mixture of 58% cis- and 42% trans-1,2-dichloroethene in rats and rabbits, no mortality was observed at the highest concentration tested of 1,000 ppm (Dow Chemical Company 1994). For oral exposure, a 7-day gavage study in mice evaluated lethality for a dose-range of 30–2,000 mg/kg/day of a mixture of the cis- and trans- isomers; the composition of the mixture was not reported (Kallman et al. 1983). No lethality was observed at doses ≤300 mg/kg/day. At a dose of 1,000 mg/kg/day, 4/7 mice died, and 100% lethality was observed in mice administered 3,000 mg/kg/day. The cause of death was not reported.

2.3 BODY WEIGHT

No studies evaluating body weight effects of inhalation, oral, or dermal exposure of humans to trans-1,2-dichloroethene, cis-1,2-dichloroethene, or mixtures of cis- and trans-1,2-dichloroethene were located.

trans-1,2-Dichloroethene. In laboratory animals, body weight effects have been evaluated for acute- and intermediate-duration inhalation and oral exposures. A developmental study evaluated maternal body weight in rats exposed to inhaled trans-1,2-dichloroethene on GDs 7–16 (Hurtt et al. 1993). In dams

exposed to 12,000 ppm, maternal body weight gain was decreased by 33.8% at the end of the exposure period on GD 16, with no effects on body weight gain observed in rats exposed to 2,000 or 6,000 ppm. The decrease in body weight gain at 12,000 ppm was accompanied by 16% decreased food intake during the exposure period, which was most likely secondary to 1,2-dichloroethene-induced narcosis. At the end of gestation, body weight of dams in all treatment groups was similar to controls. A 90-day inhalation study in rats did not observe any effects on body weight at exposure concentrations up to 4,000 ppm, the highest concentration tested (DuPont 1998). No effects on body weight were observed in 14-day gavage studies in mice at the highest doses tested of 210 mg/kg/day (Barnes et al. 1985) and 220 mg/kg/day (Munson et al. 1982). Intermediate-duration oral studies have reported conflicting results regarding effects of exposure to trans-1,2-dichloroethene on body weight. A 14-week dietary study in mice reported a 10.7% decrease in terminal body weight in females exposed to 7,925 mg/kg/day, without an accompanying decreased in feed consumption; however, no decreases in terminal body weight were observed in males at doses up to 8,065 mg/kg/day (NTP 2002). No effects on body weight were observed in other intermediate-duration oral studies in rats or mice, although these studies examined lower doses as follows (highest doses tested): 90-day drinking water study in rats (3,114 mg/kg/day in males and 2,809 mg/kg/day in females) (Hayes et al. 1987); 14-week dietary study in rats (3,245 mg/kg/day in males and 3,210 mg/kg/day in females) (NTP 2002); and 90-day drinking water study in mice (452 mg/kg/day in males and 387 mg/kg/day in females) (Barnes et al. 1985). Body weight loss was observed following a single 24-hour dermal exposure of rabbits to 5,000 mg/kg trans-1,2-dichloroethene (Brock 1990); however, the magnitude of loss and statistical significance were not reported.

cis-1,2-Dichloroethene. No studies were located regarding body weight effects in animals from inhalation or dermal exposure. No consistent or dose-related effects on terminal body weight or body weight gain were observed in a 14-day gavage study in rats. In male rats, terminal body weight in the 1,900 mg/kg/day group (highest dose tested) was decreased by 8.4% compared to controls; however, changes in body weight of <10% are not considered adverse. Terminal body weights in female rats were similar to control for all treatment groups (McCauley et al. 1990, 1995). For intermediate-duration oral exposure, a 90-day gavage study found a 37% decrease in body weight gain in male rats in the highest dose group (870 mg/kg/day), although terminal body weight was not statistically different from controls (McCauley et al. 1990, 1995). In female rats, terminal body weight and body weight gain were similar to controls in all treatment groups.

Mixed Isomers or Isomeric Composition Not Reported. No effects on body weight in rats or rabbits were observed following inhalation exposure for 2 weeks or 6 months of rats and rabbits to up to

1,000 ppm (highest concentration tested) of a mixture of 58% cis-1,2-dichloroethene and 42% trans-1,2-dichloroethene (Dow Chemical Company 1994).

2.4 RESPIRATORY

No studies evaluating respiratory effects of inhalation, oral, or dermal exposure of humans to trans-1,2-dichloroethene, cis-1,2-dichloroethene, or mixtures of cis- and trans-1,2-dichloroethene were located.

trans-1,2-Dichloroethene. Inhalation and oral exposures to trans-1,2-dichloroethene did not result in any adverse respiratory effects at the highest exposure concentrations tested: 90-day inhalation exposure of rats at concentrations up to 4,000 ppm, purity 99.86% (DuPont 1998); 14-day gavage exposure of rats to 210 mg/kg/day, purity 98% (Barnes et al. 1985); 14-week dietary exposure at doses up to 3,245 and 3,210 mg/kg/day in male and female rats, respectively, and 7,925 and 8,065 mg/kg/day in male and female mice, respectively, purity 99% (NTP 2002). A series of inhalation and oral exposure studies in rats by Freundt et al. (1977) identified adverse respiratory effects (slight capillary hyperemia of the lung with alveolar septal distention) following a single exposure to 8-hour exposure to 200 ppm and to exposures of 200 ppm for up to 16 weeks; however, these finding have not been corroborated in other studies at higher exposure levels. The Freundt et al. (1977) study had several weaknesses: pulmonary capillary hyperemia and alveolar septal distention were observed in some control rats (0, 17, or 33% in the different control groups); purity of the test substance was not reported so that potential for contaminants in the test substance was not assessed; a small number of animals (n=6) were examined; and statistical evaluation of the histological data was not presented. Given these weaknesses and lack of corroborating data, reliable NOAELs and LOAELs cannot be determined.

cis-1,2-Dichloroethene. No studies were located regarding respiratory effects of cis-1,2-dichloroethene in animals from inhalation or dermal exposure. No adverse respiratory effects were observed in rats administered cis-1,2-dichloroethene by gavage at doses of up to 1,900 mg/kg/day for 14 days or up to 870 mg/kg/day for 90 days (McCauley et al. 1990, 1995).

Mixed Isomers or Isomeric Composition Not Reported. No studies of respiratory effects of mixed cis- and trans-1,2-dichloroethene in animals were identified.

2.5 CARDIOVASCULAR

No studies evaluating cardiovascular effects of inhalation, oral, or dermal exposure of humans to trans-1,2-dichloroethene, cis-1,2-dichloroethene, or mixtures of cis- and trans-1,2-dichloroethene were located.

trans-1,2-Dichloroethene. No cardiovascular effects were observed in the following intermediate-duration inhalation or oral exposure studies of trans-1,2-dichloroethene: rats after a 90-day inhalation exposure at concentrations up to 4,000 ppm trans-1,2-dichloroethene (DuPont 1998); rats in a 14-week feeding study at doses up to 3,245 and 3,210 mg/kg/day in males and females, respectively (NTP 2002); and mice in a 14-week feeding study at doses up to 7,925 and 8,065 mg/kg/day in males and females, respectively. Freundt et al. (1977) reported histological effects in the heart (severe fibrous swelling of the myocardium and hyperemia) in rats following a single 8-hour exposure to 3,000 ppm and a single gavage dose of 1,130 mg/kg. However, given the study weaknesses, as described in Section 2.4 (Respiratory), reliable NOAELs and LOAELs cannot be determined.

cis-1,2-Dichloroethene. No studies were located regarding cardiovascular effects of inhalation or dermal exposure of animals to cis-1,2-dichloroethene. In acute- and intermediate-duration oral studies in male and female rats, no adverse cardiovascular effects were observed (McCauley et al. 1990, 1995). The highest doses tested in the studies were 1,900 mg/kg/day in the 14-day gavage study and 870 mg/kg/day in the 90-day gavage study. No additional studies evaluating cardiovascular effects of cis-1,2-dichloroethene were located.

Mixed Isomers or Isomeric Composition Not Reported. No studies of cardiovascular effects of mixed cis- and trans-1,2-dichloroethene in animals were identified.

2.6 GASTROINTESTINAL

No studies evaluating gastrointestinal effects of inhalation, oral, or dermal exposure of humans to trans-1,2-dichloroethene, cis-1,2-dichloroethene, or mixtures of cis- and trans-1,2-dichloroethene were located. Note that effects on the gallbladder are discussed under hepatic effects (Section 2.9).

trans-1,2-Dichloroethene. Little information is available regarding gastrointestinal effects of trans-1,2-dichloroethene in laboratory animals. No gastrointestinal effects were found in a 90-day inhalation studies in male and female rats at concentrations up to 4,000 ppm based on histopathological assessments (DuPont 1998). In a single dose, gavage study in rats, hyperemia of the mucosal surface of the stomach

and small intestine was observed in all animals that died (Barnes et al. 1985). The range of lethal doses was 1,600–3,500 mg/kg. Due to the lack of incidence data for death and gastrointestinal effects, reliable NOAEL and LOAEL values could not be identified. Intermediate-duration oral dietary exposure to trans-1,2-dichloroethene did not observe histopathological changes to gastrointestinal tract in rats (3,245 and 3,210 mg/kg/day in males and females, respectively) or mice (7,925 and 8,065 in males and females, respectively) (NTP 2002).

cis-1,2-Dichloroethene. No studies were located regarding gastrointestinal effects of inhalation or dermal exposure to cis-1,2-dichloroethene in animals. No gastrointestinal effects were noted in rats exposed by gavage to 1,900 mg/kg/day cis-1,2-dichloroethene for 14 days or 870 mg/kg/day cis-1,2-dichloroethene for 90 days based on histopathology (McCauley et al. 1990, 1995).

Mixed Isomers or Isomeric Composition Not Reported. No studies of gastrointestinal effects of mixed cis- and trans-1,2-dichloroethene in animals were identified.

2.7 HEMATOLOGICAL

No studies evaluating hematological effects of inhalation, oral, or dermal exposure of humans to trans-1,2-dichloroethene, cis-1,2-dichloroethene, or mixtures of cis- and trans-1,2-dichloroethene were located.

trans-1,2-Dichloroethene. Little information is available on hematological effects of inhaled trans-1,2-dichloroethene. No effects on erythrocyte count, hematocrit, or hemoglobin were observed in rats exposed to inhaled trans-1,2-dichloroethene at concentrations of 1,000 and 4,000 ppm for 90 days (DuPont 1998). A statistically significant decrease (26%) in lymphocyte count was reported after 90 days of exposure to 4,000 ppm in male rats, but not female rats (DuPont 1998). The toxicological significance of this finding is uncertain due to the small magnitude of change. Freundt et al. (1977) observed a 9% decrease in erythrocyte count, compared to controls, in rats exposed to 1,000 ppm for 8 hours (highest dose tested), with no effects observed at 200 ppm. In addition, leukocyte counts were decreased by 23% in female rats after 8 hours at 200 and 1,000 ppm. Given the weaknesses of this study (see discussion in Section 2.4), reliable NOAEL and LOAEL values cannot be determined.

Acute-duration oral exposure studies did not observe effects on erythrocyte counts or related hematological parameters. No changes to hematological parameters (hematocrit, hemoglobin concentrations, erythrocyte counts, reticulocyte count, mean cell volume, mean cell hemoglobin

concentration, platelets, white blood cell count or differentiation) were observed following dietary exposure of male and female rats for 5 days at the highest doses tested of 5,591 and 4,500 mg/kg/day in males and females, respectively (NTP 2002). At lower doses (≤240 mg/kg/day), no effects on hematocrit or blood hemoglobin were observed in male mice exposed daily by gavage for 14 days (Munson et al. 1982). No effects on leukocyte counts were observed in a 14-day gavage study in mice at 240 mg/kg/day (Munson et al. 1982). Intermediate-duration studies did not observe biologically relevant changes to hematological parameters. Barnes et al. (1985) reported a 23% increase in leukocyte counts in female mice after a 90-day exposure to 224 mg/kg/day, but not 452 mg/kg/day; differential analysis showed that the increase was primarily due to a 3-fold increase in eosinophils. This finding is not considered to be biologically significant as changes were not observed at a higher dose. Fibrinogen levels and prothrombin time were decreased by 12 and 7%, respectively, compared to controls, in mice administered 210 mg/kg/day by gavage for 14 days (Barnes et al. 1985). Results are clinically inconsistent. Decreased fibrinogen would be expected to increase prothrombin time (e.g., longer time to fibrinogen clot formation); however, prothrombin time was decreased. Munson et al. (1982) did not observe any changes to fibrinogen levels or prothrombin time in mice exposed by gavage to trans-1,2-dichloroethene for 14 days at the highest dose tested (220 mg/kg/day).

Results of intermediate-duration oral studies on erythrocyte counts and related hematological parameters are inconsistent. Hayes et al. (1987) did not observe effects on hematological parameters, including erythrocyte counts, hematocrit, and hemoglobin, in rats exposed to trans-1,2-dichloroethene in drinking water for 90 days at doses up to 2,809 and 3,114 mg/kg/day in males and females, respectively. In contrast, small, dose-related decreases in erythrocyte counts were observed in a 14-week dietary exposure study in rats at similar and lower doses (NTP 2002). Erythrocyte count was significantly decreased in male rats by 2.5, 3.6, 4.2, and 7.1%, relative to controls, at doses of 380, 770, 1,540, and 3,210 mg/kg/day, respectively; no decreases were observed at a dose of 189 mg/kg/day. Decreases in erythrocyte counts were accompanied by dose-related decreases in hematocrit and blood hemoglobin concentrations at doses ≥770 mg/kg/day. In female rats, erythrocyte counts were decreased by 3.3 and 5.1% in the 1,580 and 3,245 mg/kg/day groups, respectively; no decreases were observed at doses ≤780 mg/kg/day. Hematocrit and blood hemoglobin concentrations were decreased in the 1,580 and 3,245 mg/kg/day groups. The basis for different results of the Hayes et al. (1987) and NTP (2002) studies is not apparent. No changes in leukocyte counts were observed in intermediate-duration oral studies as follows: male and female rats exposed to 3,210 and 3,245 mg/kg/day, respectively, in the diet (NTP 2002); male mice exposed to 387 mg/kg/day for 90 days in drinking water (Barnes et al. 1985); and male and female mice exposed to 8,065 and 7,925 mg/kg/day, respectively in the diet (NTP 2002).

cis-1,2-Dichloroethene. No studies were located regarding hematological effects of inhalation or dermal exposure to cis-1,2-dichloroethene in animals. McCauley et al. (1990, 1995) evaluated hematological effects of gavage administration of cis-1,2-dichloroethene in rats exposed for 14 and 90 days. In the 14-day study, hematocrit was decreased by 11% at doses of 290, 970, and 1,900 mg/kg/day, relative to controls, in females; however, no effects were observed for erythrocyte count or hemoglobin concentration. No hematological effects were observed in males administered up to 1,900 mg/kg/day for 14 days. In the 90-day study in female rats, hematocrit was decreased by 9.9 and 6.5% at doses of 290 and 870 mg/kg/day, respectively. Erythrocyte count and hemoglobin concentration were decreased by 5.9% and 3.9%, respectively, in the 290 mg/kg/day group, but not in the 870 mg/kg/day group, indicating that these changes were not related to treatment with cis-1,2-dichloroethene. In male rats, no treatment-related effects were observed for erythrocyte count. However, hematocrit was decreased by 5.8, 8.9, and 8.9% at doses of 290, 970, and 1,900 mg/kg/day, respectively, and hemoglobin concentration was decreased by 6.0% at doses of 970 and 1,900 mg/kg/day. The toxicological significance of decreased hematocrit and hemoglobin concentration in the absence of decreased erythrocyte count is uncertain.

Mixed Isomers or Isomeric Composition Not Reported. Dow Chemical Company (1994) did not observe effects on hematocrit or hemoglobin in rats and rabbits to a mixture of 1,2-dichloroethene isomers (42% trans and 58% cis) following inhalation exposure to 1,000 ppm for 2 weeks or 6 months. No information on erythrocyte count was reported.

2.8 MUSCULOSKELETAL

No studies evaluating musculoskeletal effects of inhalation, oral, or dermal exposure of humans to trans-1,2-dichloroethene, cis-1,2-dichloroethene, or mixtures of cis- and trans-1,2-dichloroethene were located.

trans-1,2-Dichloroethene. Musculoskeletal effects of trans-1,2-dichloroethene have not been well-investigated. However, no histopathological effects in rats were observed in muscle tissue following inhalation at concentrations up to 4,000 ppm for 90 days (DuPont 1998)

cis-1,2-Dichloroethene. Acute- and intermediate-duration studies did not observe musculoskeletal effects of cis-1,2-dichloroethene based on histopathological assessments in rats exposed by gavage at doses up to 1,900 mg/kg/day for 14 days or up to 870 mg/kg/day for 90 days (McCauley et al. 1990, 1995).

Mixed Isomers or Isomeric Composition Not Reported. No studies evaluating musculoskeletal effects of mixed cis- and trans-1,2-dichloroethene or animals were identified.

2.9 HEPATIC

trans-1,2-Dichloroethene. In a case-control study of the general population (e.g., non-occupational), the risk of gallstone disease was positively associated with trans-1,2-dichloroethene levels in adipose tissue (Ji et al. 2016). The study population included 194 patients with and 190 patients without cholesterol gallstone disease. Results were stratified by quartiles (Q) based on the concentration of trans-1,2-dichloroethene in adipose tissue (ng/g lipid weight): Q1 12.82–721.7; Q2 721.7–1,351; Q3 1,351–2,558; and Q4 2,558–18,135. Odds ratios (ORs) were increased ($p \leq 0.05$) in Q2 (3.49; 95% confidence interval [CI] 1.93, 6.33), Q3 (2.38; 95% CI 1.32, 4.27), and Q4 (2.48; 95% CI 1.38, 4.46), respectively, relative to Q1. In addition, the concentration of trans-1,2-dichloroethene in adipose tissue of patients with gallstone disease (mean of 1,542 ng/g lipid weight) was significantly higher ($p=0.008$) compared to patients without gallstone disease (mean of 1,213 ng/g lipid weight).

Results of studies in laboratory animals indicate that the liver is not a sensitive target for trans-1,2-dichloroethene. No histopathological liver effects or increases in serum liver enzymes (alkaline phosphatase [AP], alanine transaminase [ALT], and aspartate transaminase [AST]) were observed in rats exposed by inhalation at concentrations up to 4,000 ppm for 90 days (DuPont 1998). Small increases in relative liver weights were observed in male and female rats at concentrations ≥200 ppm. However, the magnitude of increases was small (4–6% in males and 4–8%; in females) and increases were not dose-dependent. In the absence of histopathological changes or increased serum liver enzymes, increases in relative liver weights are not considered adverse. Freundt et al. (1977) reported fatty degeneration of liver lobules in rats exposed to 200–3,000 ppm for 8 hours and 200 ppm for up to 2 weeks. However, a statistical analysis conducted for this report showed that the incidence of lesions was not significantly different from controls. In addition, the Freundt et al. 1977 study has several weaknesses, as discussed in Section 2.4 (Respiratory).

In addition to inhalation studies conducting histopathological assessments of the liver, potential effects on the mixed function oxidase system were examined in rats (Freundt and Macholz 1978). A single 8-hour inhalation exposure to trans-1,2-dichloroethene at 200 ppm increased hexobarbital sleeping time and zoxazolamine paralysis time in rats. These effects indicate possible inhibition of the mixed function

oxidase system. Additional details on metabolism of trans-1,2-dichloroethene are provided in Section 3.1.3 (Toxicokinetics, Metabolism).

Acute- and intermediate-duration oral studies consistently show no adverse hepatic effects from exposure to trans-1,2-dichloroethene. Acute-duration studies with 14-day exposures did not find adverse liver effects in rats based on gross examination of livers in rats exposed to single doses up to 210 mg/kg/day (Barnes et al. 1985) and to 220 mg/kg/day (Munson et al. 1982). No evidence of hepatotoxicity was observed in intermediate-duration studies as follows (maximum doses tested): 3,114 and 2,809 mg/kg/day in male and female rats, respectively, in a 90-day drinking water study based on histopathology (Hayes et al. 1987); 3,210 and 3,245 mg/kg/day in male and female rats, respectively, in a 90-day dietary study based on histopathological examination (NTP 2002); 387 and 452 mg/kg/day in male and female rats, respectively, in a 90-day drinking water study based on gross necropsy (Barnes et al. 1985); and 8,065 and 7,925 mg/kg/day in male and female mice, respectively, in a 90-day dietary study based on histopathology (NTP 2002).

Other hepatic effects observed following oral exposure to trans-1,2-dichloroethene are not considered to be toxicologically significant. NTP (2002) reported increased relative liver weights (5.5–9.6% above control) in female rats at doses ≥395 mg/kg/day, although increases did not exhibit dose-dependence; no change in relative liver weight was observed in male rats. In mice, increased relative liver weights were observed in males (8.9–14% above control) and females (11% above control) at doses ≥1,900 and ≥3,760 mg/kg/day, respectively (NTP 2002). However, in the absence of gross and histopathological findings, increases in relative liver weights are not considered toxicologically significant. Other oral exposure studies did not observe increased relative liver weight in rats or mice (Barnes et al. 1985; Hayes et al. 1987). Barnes et al. (1985) observed increases in serum AP of 62 and 33% above controls at doses of 175 and 387 mg/kg/day, respectively, in male mice following 90-day exposure to trans-1,2-dichloroethene in drinking water. The increases did not exhibit dose-dependence and no changes were observed for other serum liver enzymes (lactate dehydrogenase, ALT, and AST). Therefore, the increases in serum AP activity also are not considered toxicologically significant.

cis-1,2-Dichloroethene. No studies evaluating hepatic effects of inhalation, oral, or dermal exposure of humans to cis-1,2-dichloroethene, or mixtures of cis- and trans-1,2-dichloroethene were located. In rats, histopathological assessments of the liver did not identify adverse effects of gavage exposure of rats to cis-1,2-dichloroethene following exposure to 1,900 mg/kg/day for 14 days or 870 mg/kg/day for 90 days (McCauley et al. 1990, 1995). Dose-related increases in relative liver weights were observed in male and

female rats exposed for 14 and 90 days. In the 14-day study, increases ranged from 15% at 97 mg/kg/day to 38% at 1,900 mg/kg/day. In the 90-day study, relative liver weights were increased by 15% at 32 mg/kg/day and 39% at 870 mg/kg/day (McCauley et al. 1990, 1995). Similar dose-dependent increases were observed in male rats, with increases of 16 and 38% at doses of 32 and 870 mg/kg/day, respectively (McCauley et al. 1990, 1995). However, given the absence of histopathological changes or changes in serum liver enzymes (AP, ALT, AST), the toxicological significance of increases in relative liver weights is uncertain. In rats exposed to 1,900 mg/kg/day for 14 days, but not to 870 mg/kg/day for 90 days, blood cholesterol increased by 40% compared to controls (McCauley et al. 1990, 1995). The toxicological significance of this transient effect is not established.

A single 8-hour inhalation exposure to cis-1,2-dichloroethene at 200 ppm increased hexobarbital sleeping time and zoxazolamine paralysis time in rats, indicating possible inhibition of the mixed function oxidase system (Freundt and Macholz 1978). See Section 3.1.3 (Toxicokinetics, Metabolism) for additional information on the metabolism of cis-1,2-dichloroethene.

Mixed Isomers or Isomeric Composition Not Reported. No hepatic effects were observed in rats or rabbits exposed to a mixture of 1,2-dichloroethene isomers (42% trans and 58% cis) by inhalation for 2 weeks or 6 months based on serum liver enzymes (Dow Chemical Company 1994).

2.10 RENAL

No studies evaluating renal effects of inhalation, oral, or dermal exposure of humans to trans-1,2-dichloroethene, cis-1,2-dichloroethene, or mixtures of cis- and trans-1,2-dichloroethene were located.

trans-1,2-Dichloroethene. Results of inhalation and oral exposure studies on trans-1,2-dichloroethene in animals have not identified toxicologically significant renal effects. No histopathological findings or increases in markers of decreased renal function (serum creatinine and blood urea nitrogen [BUN] levels) were observed in male or female rats following inhalation exposure of 200–4,000 ppm for 90 days (DuPont 1998). Similarly, no renal effects were observed following oral exposure, with maximum doses tested as follows: 14-day gavage at doses up to 210 mg/kg/day in mice, based on BUN (Barnes et al. 1985); 3,114 and 2,809 mg/kg/day in male and female rats, respectively, in a 90-day drinking water study based on creatinine, BUN, and gross necropsy (Hayes et al. 1987); 3,210 and 3,245 in male and female rats, respectively, in a 90-day dietary study based on histopathology and creatinine levels (NTP 2002); 387 and 452 in male and female rats, respectively, in a 90-day drinking water study based on gross

necropsy and BUN (Barnes et al. 1985); and 8,065 and 7,925 in male and female mice, respectively, in a 90-day dietary study based on histopathology (NTP 2002).

cis-1,2-Dichloroethene. No histopathological effects were observed in the kidneys following gavage exposure of rats to cis-1,2-dichloroethene at doses up to 1,900 mg/kg/day for 14 days or 870 mg/kg/day for 90 days (McCauley et al. 1990, 1995). In addition, no changes in serum creatinine were observed in male or female rats at doses up to 870 mg/kg/day for 90 days (McCauley et al. 1990, 1995). McCauley et al. (1990, 1995) observed increased relative kidney weights in male rats, but not female rats, exposed to cis-1,2-dichloroethene for 90 days, with increases ranging from 14% at 32 mg/kg/day to 27% at 870 mg/kg/day. Given the absence of histopathological and functional findings in the kidney, changes in relative kidney weights are not considered adverse.

Mixed Isomers or Isomeric Composition Not Reported. No increase in BUN was observed in rats or rabbits exposed to 1,000 ppm to a mixture of 58% cis-1,2-dichloroethene and 42% trans-1,2-dichloroethene for 14 or 90 days (Dow Chemical Company 1994).

2.11 DERMAL

No studies evaluating dermal effects of inhalation, oral, or dermal exposure of humans to trans-1,2-dichloroethene, cis-1,2-dichloroethene, or mixtures of cis- and trans-1,2-dichloroethene were located.

trans-1,2-Dichloroethene. Studies on dermal exposure of rabbits to trans-1,2-dichloroethene provide evidence of dose-dependent damage to skin. In rabbits exposed for 24 hours to 170 mg/kg trans-1,2-dichloroethene, mild-to-moderate erythema was observed; severe dermal irritation was observed at 5,000 mg/kg (Brock 1990). Following a 48-hour dermal exposure to 630 mg/kg trans-1,2-dichloroethene, mild-to-moderate erythema was observed (DuPont 1988b). DuPont (1988a) reported more severe dermal effects, including edema, necrosis, fissuring, and epidermal scaling, in rabbits exposed to 5,000 mg/kg for 24 hours. No dermal effects have been observed in inhalation or oral exposure studies of trans-1,2-dichloroethene, based on histological examinations. The highest concentrations tested are as follows: 4,000 ppm in rats in a 90-day inhalation study (DuPont 1998); 3,210 and 3,245 mg/kg/day in male and female rats, respectively, in a 90-day dietary study (NTP 2002); and 8,065 and 7,925 mg/kg/day in male and female mice, respectively, in a 90-day dietary study (NTP 2002).

cis-1,2-Dichloroethene. No dermal exposure studies of cis-1,2-dichloroethene were identified. No histopathological effects were observed in skin following gavage exposure of rats to cis-1,2-dichloroethene at doses up to 1,900 mg/kg/day for 14 days or 870 mg/kg/day for 90 days (McCauley et al. 1990, 1995).

Mixed Isomers or Isomeric Composition Not Reported. No studies evaluating dermal effects of mixed cis- and trans-1,2-dichloroethene in animals were identified.

2.12 OCULAR

trans-1,2-Dichloroethene. An experimental study in two human subjects exposed to trans-1,2-dichloroethene concentrations of 830–2,220 ppm for 30 minutes reported slight burning of the eyes (Lehmann and Schmidt-Kehl 1936). The purity of the test substance was not reported, and accurate measurement of exposure concentrations is uncertain. No additional information on exposure conditions was reported.

Exposure of laboratory animals to trans-1,2-dichloroethene in air and by instillation into the eye produces ocular irritation. In pregnant rats exposed by whole-body inhalation at 2,000, 6,000, and 12,000 ppm for 10 days, lacrimation was observed in 13/24, 22/24, and 24/24 rats, respectively, compared to 0/24 in controls (Hurtt et al. 1993). Brown, periocular staining, due to excessive lacrimation, was observed in the 6,000 ppm (18/24) and 12,000 ppm (22/24) exposure groups. Instillation of 0.01 mL trans-1,2-dichloroethene to the eyes of rabbits for 20 seconds resulted in transient severe corneal opacity, moderate iritis, and conjunctivitis (DuPont 1988c). No additional studies on potential ocular irritant effects of trans-1,2-dichloroethene were identified. Histopathological assessment did not show ocular effects in rats exposed by inhalation to concentrations up to 4,000 ppm for 90 days (DuPont 1998).

cis-1,2-Dichloroethene. No studies examining ocular effects of inhalation, oral, or ocular exposure of humans or animals to cis-1,2-dichloroethene were identified.

Mixed Isomers or Isomeric Composition Not Reported. No studies examining ocular effects of inhalation, oral, or ocular exposure of humans or animals to mixed cis- and trans-1,2-dichloroethene were identified.

2.13 ENDOCRINE

No studies evaluating endocrine effects of inhalation, oral, or dermal exposure of humans to trans-1,2-dichloroethene, cis-1,2-dichloroethene, or mixtures of cis- and trans-1,2-dichloroethene were located.

trans-1,2-Dichloroethene. No studies evaluating endocrine effects following acute-duration inhalation or oral exposure of laboratory animals were identified. No histopathological effects to the adrenal gland or thyroid were observed in rats exposed to inhaled trans-1,2-dichloroethene at concentrations up to 4,000 ppm for 90 days (DuPont 1998). Similarly, no adrenal or thyroid effects were observed in a 14-week dietary study in male and female rats at maximum doses of 3,210 and 3,245 mg/kg/day, respectively, or in male and female mice at 8,065 and 7,925 mg/kg/day, respectively (NTP 2002).

cis-1,2-Dichloroethene. Histological examination revealed no compound-related effects in the thyroid in rats exposed to cis-1,2-dichloroethene by gavage at doses up to 1,900 or 870 mg/kg/day for 14 or 90 days, respectively (McCauley et al. 1990, 1995).

Mixed Isomers or Isomeric Composition Not Reported. No studies examining endocrine effects of inhalation, oral, or dermal exposure of animals to mixed cis- and trans-1,2-dichloroethene were identified.

2.14 IMMUNOLOGICAL

No studies evaluating immunological effects of inhalation, oral, or dermal exposure of humans to trans-1,2-dichloroethene, cis-1,2-dichloroethene, or mixtures of cis- and trans-1,2-dichloroethene were located.

trans-1,2-Dichloroethene. Little information is available regarding immunological effects of inhaled trans-1,2-dichloroethene. No histological changes to the spleen, thymus, or lymph nodes were observed in rats exposed in a 90-day inhalation study at concentrations up to 4,000 ppm (DuPont 1998). Slight to severe fatty degeneration of Kupffer cells was seen after 8 hours (200, 1,000 and 3,000 ppm) and up to 16 weeks (200 ppm) of exposure to trans-1,2-dichloroethene (Freundt et al. 1977). However, an analysis conducted by ATSDR for this document shows that the incidence in treatment groups is not statistically significant compared to controls. In addition, as described in Section 2.4 (Respiratory), the study has several weaknesses; therefore, it is difficult to make conclusions on immunological effects based on these findings.

The effects of orally administered trans-1,2-dichloroethene on the immune system have been investigated in rats and mice. Endpoints examined include weights of immune organs (spleen and thymus), histopathology of immune tissues (spleen, thymus, and lymph nodes), and functional tests of cell-mediated and humoral immunity. In general, most studies do not show effects on weights of immune organs. No effects were observed on absolute and/or relative spleen or thymus weights in 14-day gavage studies at doses up to 220 mg/kg/day (Barnes et al. 1985; Munson et al. 1982; Shopp et al. 1985). For intermediate-duration exposure, no effects on absolute spleen weight were observed in 90-day drinking water studies in male mice exposed to 210 mg/kg/day (Shopp et al. 1985) or relative spleen and thymus weights in male and female mice exposed to 387 and 452 mg/kg/day respectively (Barnes et al. 1985). In the NTP (2002) 14-week dietary studies, no effects were observed on relative thymus weight in rats at doses of 3,210 and 3,245 mg/kg/day in males and females, respectively, or in mice at doses of 8,065 and 7,925 mg/kg/day in males and females, respectively. In addition, no histopathological changes in spleen, thymus, or lymph nodes were observed in rats or mice in the NTP (2002) study.

Studies assessing effects of acute-duration oral exposure to trans-1,2-dichloroethene on humoral or cell-mediated or immunity have been conducted in mice. No effects on humoral immunity were observed in mice following 14-day gavage exposure to doses up 210 mg/kg/day (Shopp et al. 1985) or 220 mg/kg/day (Munson et al. 1982). In these studies, humoral immunity was assessed by measurement of the number of spleen IgM antibody forming cells (AFCs) directed against sRBCs, serum antibody titers to sRBC, and spleen cell response to the B cell mitogen lipopolysaccharide. Cell-mediated immunity was assessed by delayed-type hypersensitivity response to sRBCs, popliteal lymph node proliferation responses to sRBC, and spleen cell response to the T-lymphocyte mitogen concanavalin A. Intermediate-duration exposure of mice to trans-1,2-dichloroethene in drinking water for 90 days decreased humoral immune function in males, but not females (Shopp et al. 1985). Suppression in humoral immunity in male mice, as measured by reductions in spleen AFCs directed against sRBCs, was observed at 175 and 387 mg/kg/day when expressed as AFC/10^6 spleen cells; the magnitude of the decrease was 26% in both groups. Other tests of immune function (spleen cell response to B cell mitogen lipopolysaccharide and hemagglutination titers) did not show suppression of humoral immunity. However, the sRBC AFC response is considered the "gold standard" for evaluating T-cell-dependent antibody responses and is considered one of the best predictors of immunotoxicity in mice (Ladics 2007). Shopp et al. (1985) did not observe any effects on cell-mediated immunity, as assessed by delayed-type hypersensitivity response to sRBC, popliteal lymph node proliferation responses to sRBC, and spleen cell response to the T-lymphocyte mitogen concanavalin A.

cis-1,2-Dichloroethene. No histopathological effects were observed in the spleen, thymus or lymph nodes of rats following gavage exposure to cis-1,2-dichloroethene at doses up to 1,900 mg/kg/day for 14 days or 870 mg/kg/day for 90 days (McCauley et al. 1990, 1995). In the same study, a slight increase in female relative thymus weight (11%) at 90 days in the highest dose group was not considered adverse given the lack of histological changes (McCauley et al. 1990, 1995).

Mixed Isomers or Isomeric Composition Not Reported. No studies examining immunological effects of inhalation, oral, or dermal exposure of animals to mixed cis- and trans-1,2-dichloroethene were identified.

2.15 NEUROLOGICAL

No reliable studies evaluating neurological effects of inhalation, oral, or dermal exposure of humans to trans-1,2-dichloroethene, cis-1,2-dichloroethene, or mixtures of cis- and trans-1,2-dichloroethene were located.

trans-1,2-Dichloroethene. Little information on neurological effects of trans-1,2-dichloroethene is available. At sublethal levels, narcosis (incidence data not reported) was observed in rats exposed by inhalation on GDs 7–16 at concentrations of 6,000 and 12,000 ppm, but not at 2,000 ppm (Hurtt et al. 1993). Lethargy was reported in 10/24 in rats exposed to 12,000 ppm but was not observed in any rats at 2,000 or 6,000 ppm (Hurtt et al. 1993). No clinical signs of neurotoxicity or histopathological effects on brain or spinal cord tissues were observed in rats exposed by inhalation for 90 days to concentrations up to 4,000 ppm (DuPont 1998). In single-dose oral lethality studies in rats, clinical signs of neurotoxicity have been observed (Barnes et al. 1985; Hayes et al. 1987); however, due to the lack of incidence data, reliable NOAEL and LOAEL values could not be identified. Hayes et al. (1987) observed clinical signs of neurotoxicity, including central nervous system depression, ataxia, and depressed respiration, at all doses (doses not reported), with dose-dependent severity. Barnes et al. (1985) observed decreased activity, ataxia, and suppressed or total lack of righting reflex in rats following doses of 1,600–3,500 mg/kg. No treatment-related effects were observed in rats or mice based on functional observational batteries, cage-side evaluations for clinical signs, or histopathological changes in neurological tissues in a 14-week dietary study in male and female rats at maximum doses of 3,210 and 3,245 mg/kg/day, respectively, or in male and female mice at 8,065 and 7,925 mg/kg/day, respectively (NTP 2002).

cis-1,2-Dichloroethene. No studies evaluating neurological effects of cis-1,2-dichloroethene in humans were located. McCauley et al. (1990) evaluated clinical signs of neurotoxicity and histopathology of brain tissue in rats exposed to cis-1,2-dichlorethene by gavage for 14 (0, 97, 290, 970, and 1,900 mg/kg/day) or 90 (0, 32, 290, and 870 mg/kg/day) days. In the 14-day study, signs of nervous system depression (lethargy and ataxia) were observed in the "high dose groups" in exposed rats. However, incidence data were not reported; therefore, NOAEL and LOAEL values could not be identified. No histopathological effects in brain tissue were observed. In rats exposed by inhalation for 90 days concentrations up to 870 ppm, no clinical signs of neurotoxicity or histopathological effects in nervous system tissues were observed (McCauley et al. 1990, 1995).

Mixed Isomers or Isomeric Composition Not Reported. Clinical signs of neurotoxicity were observed in a series of acute-duration inhalation studies of a mixture of trans- and cis-1,2-dichloroethene; the percentage of each isomer in the mixture was not reported (Dow Chemical Company 1960). Clinical signs included tremors, prone position, and/or unconsciousness, and were observed at the following exposures: 16,810 ppm for 7 hours; 29,035 ppm for 0.2, 0.5, and 1.5 hours; and 50,123 ppm for 0.1 and 0.2 hours.

Behavioral changes have been observed in mice exposed by inhalation for 4 hours to an unspecified form of 1,2-dichloroethene (De Ceaurriz et al. 1983). The reported changes consisted of a dose-related decrease in the duration of immobility in the "behavioral despair" swimming test. A 45% decrease in the total duration of immobility occurred at a concentration of 1,720 ppm. The toxicological significance of changes in the duration of swimming immobility is not known. Frantik et al. (1994) studied effects of inhalation exposure to 1,2-dichloroethene on the propagation and maintenance of the electrically evoked seizure discharge in rats and mice. The isomeric composition of 1,2-dichloroethene was not reported. The concentration of 1,2-dichloroethene evoking a 30% depression in the duration of hindlimb tonic extension in rats was 1,810 ppm and velocity of tonic extension in mice was 3,400 ppm.

2.16 REPRODUCTIVE

No studies evaluating reproductive effects of inhalation, oral, or dermal exposure of humans to trans-1,2-dichloroethene, cis-1,2-dichloroethene, or mixtures of cis- and trans-1,2-dichloroethene were located.

trans-1,2-Dichloroethene. No effects on reproductive function or tissues have been found following intermediate-duration inhalation or oral exposure to trans-1,2-dichloroethene. No histopathological

changes to male or female reproductive organs were observed in rats exposed by inhalation to 4,000 ppm for 90 days (DuPont 1998). No effects on sperm counts, sperm motility, vaginal cytology, or estrous stages or cycle length were observed in male and female rats and mice a 14-week dietary study (NTP 2002). In addition, no histopathological changes were observed in male and female reproductive tissues. The maximum doses tested were 3,210 and 3,245 mg/kg/day in male and female rats, respectively, and 8,065 and 7,925 mg/kg/day in male and female mice, respectively (NTP 2002). No treatment-related histopathological lesions in the reproductive organs were seen in male and female rats exposed to 3,114 and 2,809 mg/kg/day, respectively, of trans-1,2-dichloroethene in drinking water for 90 days (Hayes et al. 1987).

cis-1,2-Dichloroethene. No studies evaluating reproductive effects of inhalation exposure to cis-1,2-dichloroethene were identified. No treatment-related histopathological lesions in male and female reproductive organs were observed in rats administered cis-1,2-dichloroethene by gavage at maximum doses of 1,900 mg/kg/day for 14 days or 870 mg/kg/day for 90 days (McCauley et al. 1990, 1995).

Mixed Isomers or Isomeric Composition Not Reported. No studies examining reproductive effects of inhalation, oral, or dermal exposure of animals to mixed cis- and trans-1,2-dichloroethene were identified.

2.17 DEVELOPMENTAL

trans-1,2-Dichloroethene. No association between exposure to trans-1,2-dichloroethene and birth defects (neural tube defect or oral cleft defects) in children born to mothers exposed during pregnancy to trans-1,2-dichloroethene in drinking water at Marine Corps Base Camp Lejeune in North Carolina was found (Ruckart et al. 2013). Birth defects were diagnosed before 20 years of age. The study population evaluated for neural tube defect consisted of 541 children, including 15 cases of neural tube defect. The OR was 1.1 (95% CI 0.4, 3.1; p=0.85). For oral cleft defects, the study population included 550 children, with 24 cases of oral cleft defects. The OR was 0.3 (95% CI 0.2, 1.3; p=0.19). Although Ruckart et al. (2013) stated that exposure was to trans-1,2-dichlorethene, no information was reported to confirm that the trans- form was the only isomer present in drinking water. This study also assessed childhood hematopoietic cancers; these results are described in Section 2.19 (Cancer).

Developmental effects were observed in rats following inhalation exposure of dams to trans-1,2-dichloroethene on GDs 7–15 (Hurtt et al. 1993). The total number of resorptions per litter significantly increased from 0.3 in controls to 0.8 and 1.1 in the 6,000 and 12,000 ppm groups,

respectively; the number of resorptions per litter in the 2,000 ppm group was 0.6. The study authors did not consider the increase in resorptions to be biologically significant because resorption rate in controls was below historical controls, and the resorption rates in treatment groups were within historical controls for control animals. However, given the dose-dependent increase, resorptions appear to be treatment-related. In addition to resorptions, mean fetal weight in females was decreased by 5.9%, compared to controls, at 12,000 ppm; no effect on mean fetal weight was observed in males. No external, internal, or skeletal anomalies or variations were observed.

cis-1,2-Dichloroethene. No studies examining developmental effects of inhalation, oral, or dermal exposure of humans or animals to cis-1,2-dichloroethene were identified.

Mixed Isomers or Isomeric Composition Not Reported. No studies examining reproductive effects of inhalation, oral, or dermal exposure of humans or animals to mixed cis- and trans-1,2-dichloroethene were identified.

2.18 OTHER NONCANCER

trans-1,2-Dichloroethene. Increased serum glucose levels have been observed following inhalation and oral exposure to trans-1,2-dichloroethene. DuPont (1998) observed small increases in serum glucose in male and female rats exposed to 4,000 ppm for 90 days. Serum glucose was increases by 19 and 17% in males and females, respectively, compared to controls. The study authors suggest that increased serum glucose may have been related to a stress response and did not consider the increase to be toxicologically significant. An increase in serum glucose was observed in male female mice exposed to trans-1,2-dichloroethene in drinking water for 90 days (Barnes et al. 1985); the increases did not exhibit dose-dependence. In male mice exposed to 17, 175, and 387 mg/kg/day, glucose was increased by 27, 20, and 24%, respectively, compared to controls; in females, increases in the 23, 224, and 452 mg/kg/day groups were 28, 20, and 28%, respectively. In contrast, no effects on glucose levels were observed in male or female rats at doses up to 3,114 and 2,809 mg/kg/day, respectively (Hayes et al. 1987). Given that no effects on glucose levels were observed at much higher oral doses in the study by Hayes et al. (1987), the possible relationship between exposure to trans-1,2-dichloroethene and serum glucose levels is uncertain.

cis-1,2-Dichloroethene. No studies examining effects on blood or serum glucose following inhalation, oral, or dermal exposure to cis-1,2-dichloroethene were identified.

Mixed Isomers or Isomeric Composition Not Reported. No studies examining effects on blood or serum glucose following inhalation, oral, or dermal exposure to mixed cis- and trans-1,2-dichloroethene were identified.

2.19 CANCER

No studies evaluating potential carcinogenic effects of inhalation, oral, or dermal exposure of laboratory animals to trans-1,2-dichloroethene, cis-1,2-dichloroethene, or mixtures of cis- and trans-1,2-dichloroethene were located.

trans-1,2-Dichloroethene. A case-control study evaluating children born to mothers exposed during pregnancy to trans-1,2-dichloroethene in drinking water at Marine Corps Base Camp Lejeune in North Carolina did not find associations between exposure and childhood cancer (Ruckart et al. 2013). Childhood hematopoietic cancers (leukemia and non-Hodgkin's lymphoma) were diagnosed before 20 years of age. The study population included 539 children, with 13 cases of hematopoietic cancers diagnosed before 20 years of age. The OR for combined leukemia and non-Hodgkin's lymphoma was 1.5 (95% CI 0.5, 4.7; p=0.44). Ruckart et al. (2015) also did not find associations between exposure to trans-1,2-dichloroethene in drinking water at Camp Lejeune and male breast cancer. The study population consisted of 444 males, with 71 cases of breast cancer. Odds ratios for low cumulative exposure (>0–<472 ppb-months) and high cumulative exposure (≥472 ppb-months) were 0.67 (95% CI 0.03, 4.25) and 1.99 (95% CI 0.42, 7.47), respectively. Although Ruckart et al. (2013, 2015) stated that exposure was to trans-1,2-dichlorethene, no information was reported to confirm that the trans- form was the only isomer present in drinking water.

cis-1,2-Dichloroethene. No studies examining the carcinogenicity of inhalation, oral, or dermal exposure of humans or animals to cis-1,2-dichloroethene were identified.

Mixed Isomers or Isomeric Composition Not Reported. No association between occupational exposure to 1,2-dichlorethene and pancreatic cancer was observed in a population-based, case-control study of 63,097 cases and 252,386 controls (Kernan et al. 1999). Exposures were qualitatively stratified by intensity as low, medium, and high, but no quantitative exposure data were reported. For the high intensity exposure group ORs (95% CI) were: 0.5 (0.5, 1.1) for black females; 0.8 (0.5,1.2) for black males; 0.8 (0.5, 1.1) for white females; and 0.8 (0.7, 1.0) for white males.

No studies examining the carcinogenicity of inhalation, oral, or dermal exposure of animals to mixed cis- and trans-1,2-dichloroethene were identified.

Cancer Classifications. 1,2-Dichloroethene is not listed by the HHS NTP in the 15th Report on Carcinogens (NTP 2021). EPA has not classified the carcinogenicity of 1,2-dichloroethene due to inadequate information (IRIS 2010a, 2010b). IARC has not evaluated the carcinogenicity of 1,2-dichloroethene (IARC 2022).

2.20 GENOTOXICITY

Genotoxic effects of cis- and trans-1,2-dichloroethene in humans are unknown. Several studies have investigated the potential genotoxicity of trans-1,2-dichloroethene, cis-1,2-dichloroethene, and mixtures of cis- and trans-1,2-dichloroethene using *in vivo* mouse models and *in vitro* test systems (Tables 2-6 and 2-7, respectively).

Table 2-6. Genotoxicity of cis- and trans-1,2-Dichloroethene *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
trans-1,2-Dichloroethene			
Mammalian systems:			
Mouse bone marrow	Chromosomal aberrations	–	Cerna and Kypenova 1977
Mouse bone marrow	Chromosomal aberrations	–	NTP 2002
Mouse bone marrow	Sister chromatid exchange	–	NTP 2002
Peripheral blood erythrocytes (mouse)	Micronuclei frequency	–	NTP 2002
Host-mediated assays:			
Salmonella typhimurium (mouse host-mediated assay)	Gene mutation	–	Cerna and Kypenova 1977
S. cerevisiae D7 (mouse host-mediated assay)	Gene mutation	–	Cantelli-Forti and Bronzetti 1988
S. cerevisiae D7 (mouse host-mediated assay)	Gene mutation	–	Bronzetti et al. 1984
S. cerevisiae D7 (mouse host-mediated assay)	Gene conversion	–	Bronzetti et al. 1984
S. cerevisiae D7 (mouse host-mediated assay)	Gene conversion	–	Cantelli-Forti and Bronzetti 1988
cis-1,2-Dichloroethene			
Mammalian systems:			
Mouse bone marrow	Chromosomal aberrations	+	Cerna and Kypenova 1977
Mouse bone marrow	Chromosomal aberrations	–	NTP 2002

Table 2-6. Genotoxicity of cis- and trans-1,2-Dichloroethene *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
Mouse bone marrow	Sister chromatid exchange	–	NTP 2002
Host-mediated assays:			
S. typhimurium (mouse host-mediated assay)	Gene mutation	+	Cerna and Kypenova 1977
Saccharomyces. cerevisiae D7 (mouse host-mediated assay)	Gene mutation	+	Cantelli-Forti and Bronzetti 1988
Saccharomyces. cerevisiae D7 (mouse host-mediated assay)	Gene mutation	+	Bronzetti et al. 1984
S. cerevisiae D7 (mouse host-mediated assay)	Gene conversion	+	Bronzetti et al. 1984
S. cerevisiae D7 (mouse host-mediated assay)	Gene conversion	–	Cantelli-Forti and Bronzetti 1988
Mixed isomers or isomeric composition not reported[a]			
Mammalian systems:			
Mouse bone	Chromosomal aberrations	–	Crebelli et al. 1999

[a]Mixture consisted of trans- and cis-1,2-dichloroethene isomers, the percentage of each isomer was not reported
– = negative result; + = positive result

Table 2-7. Genotoxicity of cis- and trans-1,2-Dichloroethene *In Vitro*

		Results		
		Activation		
Species (test system)	Endpoint	With	Without	Reference
trans-1,2-Dichloroethene				
Prokaryotic organisms:				
Escherichia coli K12	Gene mutation	–	–	Greim et al. 1975
E. coli K12	Gene mutation	–	–	Cantelli-Forti and Bronzetti 1988
Salmonella typhimurium TA1950, TA1951, TAA1952	Gene mutation	ND	–	Cerna and Kypenova 1977
S. typhimurium	Gene mutation	–	–	NTP 2002
Eukaryotic organisms:				
Fungi:				
Saccharomyces. cerevisiae D7	Gene mutation	–	–	Bronzetti et al. 1984
S. cerevisiae D7	Gene mutation	–	–	Galli et al. 1982
S. cerevisiae D7	Gene conversion	–	–	Bronzetti et al. 1984
S. cerevisiae D7	Gene conversion	–	–	Galli et al. 1982
S. cerevisiae D7	Gene mutation	–	–	Koch et al. 1988
S. cerevisiae D61.M	Aneuploidy	+	+	Koch et al. 1988

Table 2-7. Genotoxicity of cis- and trans-1,2-Dichloroethene *In Vitro*

Species (test system)	Endpoint	Results: Activation With	Results: Activation Without	Reference
Mammalian cells:				
Chinese hamster CHL cells	Chromosomal aberrations	–	–	Sawada et al. 1987
Chinese hamster CHO cells	Chromosomal aberrations	–	–	NTP 2002
Chinese hamster CHL cells	Sister chromatid exchange	–	–	Sawada et al. 1987
Chinese hamster CHO cells	Sister chromatid exchange	+/–	–	NTP 2002
Rat hepatocytes	Unscheduled DNA synthesis	NA	–	Costa and Ivanetich 1984
cis-1,2-Dichloroethene				
Prokaryotic organisms:				
E. K12	Gene mutation	–	–	Greim et al. 1975
E. coli K12	Gene mutation	–	–	Cantelli-Forti and Bronzetti 1988
S. typhimurium TA1950, TA1951, TAA1952	Gene mutation	ND	–	Cerna and Kypenova 1977
S. typhimurium TA97, TA98, TA100, TA1535, TA1537	Gene mutation	–	–	NTP 2002
S. typhimurium TA97, TA98, TA100, TA1535, TA1537	Gene mutation	–	–	Zeiger et al. 1988
Eukaryotic organisms:				
Fungi:				
Saccharomyces cerevisiae D7	Gene mutation	+	–	Bronzetti et al. 1984
S. cerevisiae D7	Gene mutation	–	–	Galli et al. 1982
S. cerevisiae D7	Gene conversion	–	–	Galli et al. 1982
Mammalian cells:				
Chinese hamster CHL cells	Chromosomal aberrations	–	–	Sawada et al. 1987
Chinese hamster CHO cells	Chromosomal aberrations	–	–	NTP 2002
Chinese hamster CHL cells	Sister chromatid exchange	–	–	Sawada et al. 1987
Chinese hamster CHO cells	Sister chromatid exchange	+/–	+	NTP 2002
Rat hepatocytes	Unscheduled DNA synthesis	NA	–	Costa and Ivanetich 1984

Table 2-7. Genotoxicity of cis- and trans-1,2-Dichloroethene *In Vitro*

Species (test system)	Endpoint	Results: Activation With	Results: Activation Without	Reference
Mixed isomers or isomeric composition not reported[a]				
Prokaryotic organisms:				
S. typhimurium TA98, TA100, TA1535, TA1537	Gene mutation	–	–	NTP 2002
S. typhimurium TA98, TA100, TA1535, TA1537	Gene mutation	–	–	Mortelmans et al. 1986
Eukaryotic organisms				
Fungi:				
Aspergillus nidulans	Aneuploidy	ND	–	Crebelli et al. 1995
Mammalian cells:				
Chinese hamster CHO cells	Chromosomal aberrations	–	–	NTP 2002
Chinese hamster CHO cells	Sister chromatid exchange	+	+	NTP 2002
Peripheral blood lymphocytes (human)	Micronuclei frequency	+	+	Tafazoli and Kirsch-Volders 1996
Peripheral blood lymphocytes (human)	DNA damage	+	+	Tafazoli and Kirsch-Volders 1996

[a]Mixture consisted of both trans- and cis-1,2-dichloroethene, the percentage of each isomer was not reported

+ = positive result; – = negative result; +/– = equivocal result; CHL = Chinese hamster lung fibroblast; CHO = Chinese hamster ovary; DNA = deoxyribonucleic acid; NA = not applicable; ND = not determined; NR = not reported

trans-1,2-Dichloroethene. trans-1,2-Dichloroethene did not produce genotoxic effects when tested *in vivo* or *in vitro*. No increases in chromosome aberrations or sister chromatid exchanges were observed in bone marrow cells of mice following an intraperitoneal (i.p.) injection of up to 2,000 mg/kg trans-1,2-dichloroethene (Cerna and Kypenova 1977; NTP 2002). Peripheral blood from mice fed up to 50,000 ppm of trans-1,2-dichloroethene for 14 weeks showed no increase in micronuclei frequency (NTP 2002). No alterations in the occurrence of gene mutations or gene conversions were observed in bacterial systems (Cantelli-Forti and Bronzetti 1988; Cerna and Kypenova 1977; Greim et al. 1975; NTP 2002) or fungi (Bronzetti et al. 1984; Galli et al. 1982; Koch et al. 1988), except for one study that reported increased aneuploidy in *Saccharomyces cerevisiae* D61.M with and without activation (Koch et al. 1988). In mammalian cells, no increases in chromosomal aberrations or sister chromatid exchanges were seen in Chinese hamster cell lines with or without activation (Sawada et al. 1987 and NTP 2002), or in unscheduled deoxyribonucleic acid (DNA) synthesis in rat hepatocytes (Costa and Ivanetich 1984).

cis-1,2-Dichloroethene. Reports on the genotoxic effects of cis-1,2-dichlorethene have been inconsistent. Repeated i.p. injections of cis-1,2-dichloroethene (1/6 LD_{50}) produced chromosomal aberrations in mouse bone marrow cells (Cerna and Kypenova 1977), whereas a single i.p. injection up to 2,000 mg/kg did not result in an increase in chromosomal aberrations or sister chromatid exchanges in mouse bone marrow (NTP 2002). cis-1,2-Dichloroethene was found to be mutagenic in the host-mediated assay using a series of *Salmonella* tester strains and *S. cerevisiae* D7 in mice (Bronzetti et al. 1984; Cantelli-Forti and Bronzetti 1988; Cerna and Kypenova 1977). Results of most *in vitro* studies show that cis-1,2-dichloroethene is not genotoxic. No increase in gene mutations were seen in *Escherichia coli* (Cantelli-Forti and Bronzetti 1988; Greim et al. 1975), *Salmonella* (Cerna and Kypenova 1977; NTP 2002; Zeiger et al. 1988) or *Saccharomyces* (Galli et al. 1982) with or without activation. The one exception was the Bronzetti et al. (1984) study, which reported increased mutations in *Saccharomyces* in the presence of metabolic activators. In Chinese hamster cells, cis-1,2-dichloroethene, with or without activation, did not increase the number of chromosomal aberrations (NTP 2002; Sawada et al. 1987). Sawada et al. (1987) reported no increase in sister chromatid exchanges in Chinese hamster lung fibroblast cells in the presence or absence of activation, whereas NTP (2002) showed increased exchanges in Chinese hamster ovary cells in the absence of activation. cis-1,2-Dichloroethene did not induce unscheduled DNA synthesis in rat hepatocytes *in vitro* (Costa and Ivanetich 1984).

Mixed Isomers or Isomeric Composition Not Reported. Limited *in vivo* data are available regarding genotoxicity of mixtures of cis- and trans-1,2-dichloroethene. For all studies cited below, the mixture investigated consisted of both trans- and cis-1,2-dichloroethene; however, the percentage of each isomer was not reported. No increase in chromosomal aberrations was seen in the bone marrow of CD-1 mice following an i.p. injection of a mixture of cis- and trans-1,2-dichloroethene (Crebelli et al. 1999). Results from studies investigating genotoxic effects *in vitro* are inconsistent. Mixed isomers were shown not to be mutagenic in *Salmonella* (Mortelmans et al. 1986; NTP 2002) and did not increase aneuploidy in *Aspergillus* (Crebelli et al. 1995). However, in Chinese hamster ovary cells, an increase in sister chromatid exchanges was observed following exposure to a mixture of cis- and trans-1,2-dichloroethene, although chromosomal aberrations were not increased (NTP 2002). In isolated human peripheral blood lymphocytes, DNA damage and micronuclei frequency were increased after exposure to mixed isomers of 1,2-dichloroethene (Tafazoli and Kirsch-Volders. 1996).

2.21 MECHANISM OF TOXICITY

The mechanism of toxicity of 1,2-dichloroethene has not been determined. As reviewed in Section 3.1.3 (Toxicokinetics, Metabolism), studies conducted in rats have shown that 1,2-dichloroethene can alter cytochrome P450 (CYP) levels and mixed-function oxidase activities. Inhibition of CYP2E1 activity has been attributed to formation of reactive metabolites of 1,2-dichloroethene (Lilly et al. 1998). Metabolites that could possibly contribute to health effects include epoxides, dichloroacetaldehyde, dichloroethanol, and dichloroacetic acid. The Integrated Risk Information System (IRIS 2010a, 2010b) noted that metabolites could possibly bind to cell components.

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

3.1 TOXICOKINETICS

Overview

- Information on the toxicokinetics of cis- and trans-1,2-dichloroethene comes mainly from inhalation studies conducted in rats.
- The cis- and trans- isomers have distinct toxicokinetics.

Absorption

- Studies conducted in rats indicate relatively rapid absorption of inhaled 1,2-dichloroethene with air:blood equilibrium occurring within 1–2 hours following initiation of a constant exposure.
- Continued inhalation absorption following equilibrium is driven by elimination of 1,2-dichloroethene, primarily by metabolism.
- The blood:air partition coefficient for cis-1,2-dichloroethene is higher than that of trans-1,2-dichloroethene.
- No studies were located that described amounts or kinetics of absorption of cis- or trans-1,2-dichloroethene following oral exposure.
- No studies were located that described amounts or kinetics of absorption of cis- or trans-1,2-dichloroethene following dermal exposure.

Distribution

- No studies were located regarding the distribution of cis- and trans-1,2-dichloroethene following exposure by any route.
- Tissue:air partition coefficients suggest that both isomers will enter most tissues and that the highest concentrations are likely to be observed in adipose.

Metabolism

- Metabolism is the primary mechanism of elimination of absorbed 1,2-dichloroethene.
- 1,2-Dichloroethene is metabolized by the microsomal CYP monooxygenase enzyme system in the liver.
- 1,2-Dichloroethene exhibits dose-dependent metabolic clearance resulting from substrate saturation and suicide inhibition of CYP.
- 1,2-Dichloroethene induces CYP isozymes in liver and these effects on CYP are sex-dependent in rats.

- trans-1,2-Dichloroethene is a more potent inhibitor of CYP than cis-1,2-dichloroethene and is more slowly metabolized than cis-1,2-dichloroethene.

- Zero-order metabolic elimination (saturation) occurs with exposures to 1,000 ppm cis-1,2-dichloroethene and 25 ppm trans-1,2-dichloroethene.

Excretion

- No studies were located regarding the excretion of 1,2-dichloroethene in humans or animals following exposure by any route.

Toxicokinetics Models

- A physiologically based pharmacokinetic (PBPK) model has been developed for simulating the kinetics of inhalation uptake, metabolic elimination, and inhibition of metabolism of cis- and trans-1,2-dichloroethene in rats.

- Generic PBPK models have been used to simulate steady-state blood 1,2-dichloroethene concentrations and blood concentration area under the curve (AUC) in humans.

3.1.1 Absorption

Closed chamber gas-uptake studies performed on rats have examined the kinetics of absorption and elimination of inhaled cis- and trans-1,2-dichloroethene (Andersen et al. 1980; Clewell and Andersen 1994; Filser and Bolt 1979). The kinetics of uptake from the chamber exhibited a rapid phase and a slow phase. The rapid phase of uptake, reflecting the kinetics of absorption and distribution, occurred within 1–2 hours. The slower phase, reflecting the kinetics of metabolism, exhibited saturation kinetics. The rate for the slower phase is dose-dependent, consistent with saturable metabolism and inhibition of metabolism (Clewell and Andersen 1994; Lilly et al. 1998).

Absorption of inhaled 1,2-dichloroethene will be governed, in part, by the blood:air partition coefficient. Several studies have measured blood:air partition coefficients for 1,2-dichloroethene (Gargas et al. 1988, 1989; Sato and Nakajima 1979). The blood:air partition coefficient for cis-1,2-dichloroethene is higher (approximately 20) than that of trans-1,2-dichloroethene (approximately 10) (Gargas et al. 1989).

No studies were located that described amounts or kinetics of absorption of cis- or trans-1,2-dichloroethene following oral or dermal exposure.

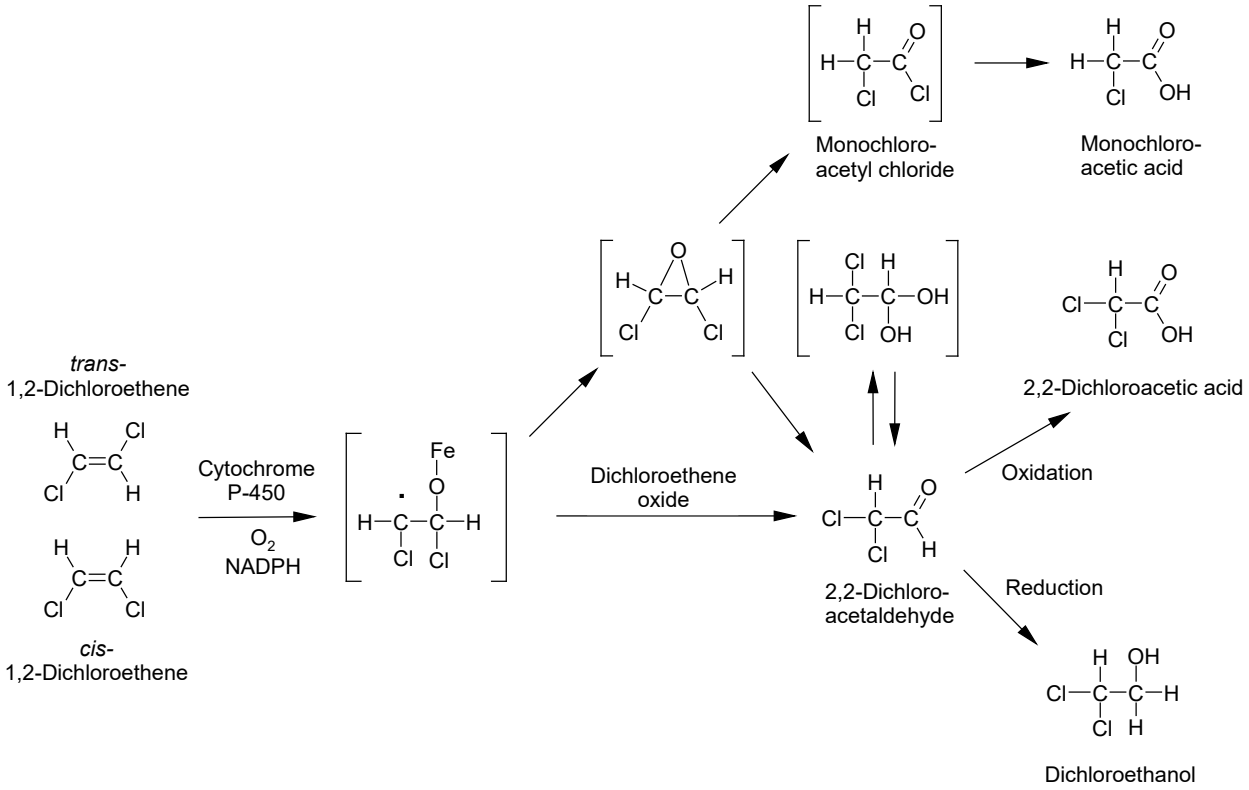
3.1.2 Distribution

No studies were located regarding the distribution of cis- and trans-1,2-dichloroethene following exposure by any route. However, tissue:air partition coefficients suggest that both isomers will enter most tissues and that the highest concentrations are likely to be observed in adipose. Gargas et al. (1988, 1989) determined rat tissue:air partition coefficients for cis- and trans-1,2-dichloroethene. The partition coefficients for cis-1,2-dichloroethene were as follows: blood 21.6 (±2.0), 0.9% saline 3.25 (±0.12), olive oil 278 (±6), fat 227 (±11), liver 15.3 (±11), and muscle 6.09 (±1.02). The coefficients for trans-1,2-dichloroethene were: blood 9.58 (±0.94), 0.9% saline 1.41 (±0.04), olive oil 178 (±6), fat 148 (±11), liver 8.96 (±0.61), and muscle 3.52 (±0.54).

3.1.3 Metabolism

Metabolism of 1,2-dichloroethene is initially catalyzed by hepatic microsomal CYP (Costa and Ivanetich 1982, 1984). The reaction is catalyzed by multiple isozymes, including the CYP2E1 and CYP34A (Costa and Ivanetich 1982; Lilly et al. 1998). Although there is no direct evidence, studies on the synthesis of epoxides suggest that metabolism involves epoxidation of the ethylene double bond, forming dichlorinated epoxides (Figure 3-1). Dichlorinated epoxides, in turn, can undergo a non-enzymatic rearrangement. Studies on the metabolism of 1,2-dichloroethene by hepatic microsomes and hepatocytes provide evidence to suggest that dichloroacetaldehyde is the predominant metabolite of microsomal CYP and that it, in turn, is extensively converted to dichloroethanol and dichloroacetate by cytosolic and/or mitochondrial aldehyde and alcohol dehydrogenases present in hepatocytes (Costa and Ivanetich 1982, 1984; Leibman and Ortiz 1977). Dechlorination of dichloroacetate is catalyzed by glutathione S-transferase (Costa and Ivanetich 1982). This is consistent with the report that both cis- and trans-1,2-dichloroethene were converted to dichloroethanol and dichloroacetic acid by perfused rat liver (Bonse et al. 1975).

Figure 3-1. Postulated Metabolic Scheme for 1,2-Dichloroethene



Source: Costa and Ivanetich 1982

Similarities and differences have been observed in the metabolism of cis- and trans-1,2-dichloroethene. Both isomers have been shown to bind to the active site of hepatic CYP (Costa and Ivanetich 1982). In addition, classic inhibitors of CYP have been shown to inhibit the production of dichloroacetaldehyde from both isomers. The binding and metabolism of 1,2-dichloroethene do not appear to be specific for any one form of CYP. cis-1,2-Dichloroethene had a 4-fold greater rate of turnover in hepatic microsomes *in vitro* than trans-1,2-dichloroethene. This is consistent with studies on isolated perfused rat livers, where metabolism of cis-1,2-dichloroethene occurred at a greater rate than metabolism of trans-1,2-dichloroethene (Bonse et al. 1975). In addition, differences between cis- and trans-1,2-dichloroethene in the rates of formation of dichloroethanol and dichloroacetic acid have been reported in rat hepatocytes (Costa and Ivanetich 1984).

Studies conducted in rats have shown that 1,2-dichloroethene can alter CYP levels and mixed-function oxidase activities. Effects observed in rats have included inhibition (Freundt and Macholz 1978; Hanioka et al. 1998; Lilly et al. 1998; McMillan 1986; Nakahama et al. 2000), decreased expression (Hanioka et al. 1998; Nakahama et al. 2000), and induction (Bronzetti et al. 1984; Hanioka et al. 1998; Paolini et al.

1992). These different effects are specific to CYP isozymes, dose levels, and sex. Treatment of male rats with cis- or trans-1,2-dichloroethene decreased expression of hepatic CYP3A, CYP2B, CYP2C, and CYP2E isoforms (Hanioka et al. 1998; Nakahama et al. 2000). Inhibition of CYP2E1 activity has been attributed to formation of reactive metabolites of 1,2-dichloroethene that disrupt the active site of the enzyme (*suicide inhibition*) (Lilly et al. 1998). trans-1,2-Dichloroethene was a more potent inhibitor of CYP2E1 than cis-1,2-dichloroethene in male rats (Lilly et al. 1998). cis-1,2-Dichloroethene decreased expression of hepatic CYP1A1/2 and CYP2B1/2, whereas trans-1,2-dichloroethene increased expression of these isozymes in male rats (Hanioka et al. 1998). Changes in CYP activities (increased or decreased) resulting from exposure to cis- or trans-1,2-dichloroethene were different in male and female rats (Hanioka et al. 1998). For example, cis-1,2-dichloroethene reduced expression of CYPA1/2 in male rats, but increased expression of the isozyme in female rats. Expression of CYP2E1 was increased in female rats but decreased in male rats. Freundt and Macholz (1978) demonstrated that cis-1,2-dichloroethene was a more potent inhibitor of metabolism of hexobarbital in rats. Inhibition of N- and O-demethylation by cis- and trans-1,2-dichloroethene was competitive and reversible in rat liver microsomes (Freundt and Macholz 1978).

The metabolic elimination of 1,2-dichloroethene has been described as a saturable, dose-dependent process (Andersen et al. 1980; Clewell and Andersen 1994; Filser and Bolt 1979). The primary basis for this conclusion is from observations made in rats of the kinetics of uptake of 1,2-dichloroethene from closed exposure chambers (Andersen et al. 1980; Clewell and Andersen 1994; Filser and Bolt 1979). An initial rapid “equilibrium” phase of uptake results from distribution of 1,2-dichloroethene into blood and tissues. This is followed by a slower “elimination” phase. The slow-phase kinetics has been used to estimate rates of metabolism of 1,2-dichloroethene, with the assumption that all slow-phase elimination results from metabolism. The rate of the elimination phase is dose-dependent; first-order at low exposure concentrations and zero-order and higher at “saturating” concentrations (e.g., 1,000 ppm) (Filser and Bolt 1979). Saturation is thought to reflect a combination of full occupancy of the enzyme coupled with inhibition of the enzyme from reactive intermediates (Lilly et al. 1998). Lilly et al. (1998) estimated the K_M, V_{max}, and inhibition constant (K_d) for metabolic elimination of cis- and trans-1,2-dichloroethene (Table 3-1). Based on the estimated K_M and V_{max}, 90% of the V_{max} was estimated to be achieved at an exposure concentration of 1,800 ppm for cis-1,2-dichloroethene and 800 ppm for trans-1,2-dichloroethene. However, Lilly et al. (1998) also concluded that trans-1,2-dichloroethene is a more potent inhibitor of CYP than cis-1,2-dichloroethene and, as a result, saturation of metabolism can occur at lower exposures to trans-1,2-dichloroethene than predicted from the K_M. If enzyme inhibition is not considered, the estimated V_{max} for trans-1,2-dichloroethene is substantially lower than cis-

1,2-dichloroethene (2.4 and 0.67 mg/kg/hour, respectively) (Csandy et al. 1995). The higher V_{max} for cis-1,2-dichloroethene is consistent with the higher rate of metabolism of cis-1,2-dichloroethene relative to trans-1,2-dichloroethene by rat liver microsomes (Costa and Ivanetich 1982) and by isolated perfused liver (Bonse et al. 1975).

Table 3-1. Optimized Values for Metabolism Parameters in the Lilly et al. (1998) Rat PBPK Model of 1,2-Dichloroethene[a]

	V_{max} (mg/hour/kg body weight)	K_M (mg/L, ppm)	K_d (mg/hour/hour)	K_{de} ($hour^{-1}$)
cis-1,2-Dichloroethene	4.53±0.12	0.19±0.01 (48±3)	2.07±0.05	0.025±0.001
trans-1,2-Dichloroethene	4.27±0.04	0.08±0.01 (20±3)	496±2.16	0.026±0.001

[a]Shown are mean ± standard deviation.

K_d = enzyme inhibition coefficient; K_{de} = enzyme degradation coefficient; K_M = half-saturation concentration; PBPK = physiologically based pharmacokinetic; V_{max} = maximum rate of metabolism

The importance of CYP2E1 and glutathione S-transferase in the metabolism of 1,2-dichloroethene raises the possibility of population genetic polymorphisms in these two enzyme systems contributing to variability in 1,2-dichloroethene metabolism in humans (Blackburn et al. 2000, 2001; Lipscomb et al. 1997).

3.1.4 Excretion

No studies were located regarding the excretion of 1,2-dichloroethene in humans or animals following exposure by any route.

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.

Lilly et al. (1998) Model

Description. Lilly et al. (1998) developed a PBPK model for simulating the kinetics of inhalation uptake and elimination of cis- and trans-1,2-dichloroethene in rats. The model includes compartments representing lung, fat, liver, and lumped compartments representing all other rapidly perfused tissues and all other slowly perfused tissues. Exchange of 1,2-dichloroethene between air and blood and blood and tissues is assumed to be flow-limited and governed by tissue blood flow and tissue:blood partition coefficients. Elimination of 1,2-dichloroethene is simulated as a capacity limited metabolism (CYP2E1) governed by a V_{max} (mg/kg/hour) and K_M (mg/L). Inhibition of metabolism is simulated as a zero-order loss of activity (mg/hour/hour) and enzyme re-synthesis was simulated as a first-order order process ($hour^{-1}$).

Calibration and Evaluation. Blood:air and tissue:blood partition coefficients were from Gargas et al. (1989). Initial values for metabolism parameters, V_{max} and K_M, were estimated from closed chamber experiments (Gargas et al. 1988). Metabolic parameters were recalibrated to fit observations of rates of uptake of 1,2-dichloroethene by rats in closed exposure chambers (Lilly et al. 1998). Various approaches to modeling inhibition of metabolism were explored. The best fit to the closed chamber observations for both isomers was obtained with a model in which metabolism produces a reactive intermediate that binds to and inactivates the enzyme-substrate complex. The optimized values for V_{max} and K_M and the enzyme inhibition constant (K_d) are provided in Table 3-1. These values suggest that trans-1,2-dichloroethene is a more potent inhibitor of CYP2E1 than cis-1,2-dichloroethene.

Other Modeling Approaches

Aylward et al. (2010). Aylward et al. (2010) developed a model for simulating the steady-state concentration of cis- and trans-1,2-dichloroethene in rats and humans. The model was a steady-state solution to a generic multi-compartment PBPK model. At steady state, the multi-compartment model was reduced to parameters representing alveolar ventilation, cardiac output, liver blood flow, blood:air partition coefficient, liver:blood partition coefficient, and first order metabolism clearance coefficients (V_{max}/K_M). The rat model was extrapolated to humans by replacing the blood:air partition coefficient for humans (Gargas et al. 1989), and allometrically scaling the rat V_{max} by body weight ($BW^{0.7}$). Evaluation

of the human model was not reported. Aylward et al. (2010) applied the human model to predicting the blood/dose slope associated with continuous steady state exposures that would result in hepatic venous blood concentrations well below saturation of metabolism (i.e., $<0.1xK_M$). The predicted inhalation slopes were 3.3 μg/L per mg/m^3 (13 μg/L per ppm) for cis-1,2-dichloroethene and 1.9 μg/L per mg/m^3 (7.5 μg/L per ppm) for trans-1,2-dichloroethene. The predicted oral slopes were 17 μg/L per mg/kg/day (absorbed dose) for cis-1,2-dichloroethene and 3.4 μg/L per mg/kg/day for trans-1,2-dichloroethene.

Peyret and Krishnan (2012). Peyret and Krishnan (2012) utilized a generic PBPK model to predict the blood concentration AUC of cis- and trans-1,2-dichloroethene in humans. Blood:air and tissue:blood partition coefficients were based on Gargas et al. (1989). First-order metabolism clearance coefficients (V_{max}/K_M) were predicted from quantitative structure-activity relationship (QSAR) modeling of reported clearance coefficients estimated in rats for a set of 26 volatile organic compounds (VOCs), with the V_{max} allometrically scaled by body weight ($BW^{0.75}$). The clearance coefficients were used in the PBPK model to calculate the metabolic clearance of 1,2-dichloroethene in the liver at levels of hepatic venous blood concentrations well below saturation (e.g., inhalation exposures to 1 ppm). An evaluation of the model for predicting blood concentrations of 1,2-dichloroethene in humans was not reported.

3.1.6 Animal-to-Human Extrapolations

No studies were located regarding the toxicokinetics of 1,2-dichloroethene in humans. Toxicokinetic studies conducted in rats suggest that animal-to-human extrapolation of dose-response relationships should consider several factors: (1) dose-dependent metabolic clearance resulting from enzyme saturation and suicide inhibition; (2) production of reactive intermediates which may contribute to some forms of toxicity; and (3) sex-dependent effects on CYP mixed-function oxidase activities (see Section 3.1.3). Dose-dependent clearance is particularly important for animal-to-human extrapolation of dose-response relationships. Many studies conducted in animals have observed adverse effects at inhalation exposures predicted to be close to or above saturating levels for metabolic clearance of cis- and trans-1,2-dichloroethene (e.g., ≥800 ppm). Linear extrapolation of responses to lower dose levels, below saturation, would be highly uncertain and alternative approaches such as PBPK modeling would be needed to support such extrapolations. A PBPK model that simulates dose-dependent clearance of cis- and trans-1,2-dichloroethene in rats has been developed (see Section 3.1.5).

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

It is not known if children are more susceptible to toxic effects of 1,2-dichloroethene, and few studies have evaluated effects in immature offspring. No increase in the risk of birth defects (neural tube defect or oral cleft defects) or childhood hematopoietic cancers were observed in an epidemiological study in children born to women exposed to 1,2-dichlorethane in their drinking water during pregnancy (Ruckart et al. 2013). Gestational exposure of rats to inhaled trans-1,2-dichloroethene resulted in an increased number of resorptions and decreased fetal weight; no malformations or variations were identified (Hurtt et al. 1993). The significance of these findings to humans is unknown.

As discussed in Section 3.1.3 (Toxicokinetics, Metabolism), metabolism of 1,2-dichloroethene involves multiple CYP isozymes, including CYP2E1 and CYP34A (Costa and Ivanetich 1982, 1984; Lilly et al. 1998). Individuals with underlying liver disease may have a decreased capacity to metabolize 1,2-dichloroethene. In addition, CYP2E1 can be induced by fasting and diabetes (Rannug et al. 1995). In children, CYP enzymes may not have the same metabolic capacity as adults, leading to potentially higher blood levels; however, no information on metabolism of 1,2-dichloroethene isomers is available in infants, children, or immature animals. CYP2E1 and glutathione S-transferase zeta (GSTZ) exist in different polymorphic forms. Metabolic activity may vary between specific polymorphisms of these enzymes, resulting in altered blood levels of 1,2-dichloroethene and its metabolites.

No populations with unusual susceptibility to the health effects of 1,2-dichloroethene were identified. As discussed in Section 2.18 (Other Noncancer), small increases in serum glucose levels were observed in mice following a 90-day exposure to trans-1,2-dichloroethene in drinking water (Barnes et al. 1985); the increases did not exhibit dose-dependence. Although the toxicological significance of this finding is uncertain, an association between exposure to trans-1,2-dichloroethene and altered glucose metabolism cannot be ruled out. Therefore, individuals with diabetes may be more susceptible to trans-1,2-dichloroethene exposure. Studies have also shown that exposure to trans- and cis-1,2-dichloroethene can decrease erythrocyte counts (see Section 2.7, Hematological). Therefore, individuals with anemia may have increased susceptibility to 1,2-dichloroethene. Additionally, immunocompromised individuals may have increased susceptibility to 1,2-dichloroethene based on the findings of impaired immune response in mice exposed to trans-1,2-dichloroethene.

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

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

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to 1,2-dichloroethene 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 1,2-dichloroethene 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 (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 1,2-Dichloroethene 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

1,2-Dichloroethene can be measured in blood and expired air. Blood 1,2-dichloroethene levels have been used to quantify exposure in the U.S. general population (Ashley et al. 1994; CDC 2021). cis-1,2-Dichloroethene can be measured in expired air; however, its usefulness as a biomarker may be limited since a half-life of <30 minutes was estimated in a study of two volunteers (Pleil and Lindstrom 1997).

3.3.2 Biomarkers of Effect

There currently are no biomarkers of effect available to characterize effects specifically caused by 1,2-dichloroethene in humans. Effects observed following exposure to 1,2-dichloroethene can be observed with many chemicals, and there is not an effect that is unique to 1,2-dichloroethene.

3.4 INTERACTIONS WITH OTHER CHEMICALS

No studies were located regarding possible interactions between 1,2-dichloroethene and other chemicals that are likely to be found with 1,2-dichloroethene in the environment, workplace, or at hazardous waste sites.

CYP isozymes, glutathione s-transferases and glutathione are important for the metabolism of 1,2-dichlorethene (see Section 3.1.3). Chemicals that induce or inhibit CYP isozymes or decrease glutathione concentrations (e.g., ethanol) may alter metabolism and affect the toxicity of 1,2-dichloro-ethene. However, no *in vivo* studies were located investigating potential interactions. In an *in vitro* study, rat pancreatic tumor cells exposed to trans-1,2-dichloroethene alone or in combination with ethanol did not affect cell proliferation, viability, or fatty acid ethyl ester production of the cells (Bhopale et al. 2014).

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

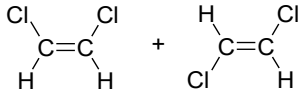
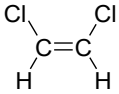
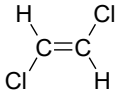
4.1 CHEMICAL IDENTITY

Information regarding the chemical identity of 1,2-dichloroethene is in Table 4-1.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of 1,2-dichloroethene is in Table 4-2. There are two geometric isomers of 1,2-dichloroethene: the cis- form and the trans- form. The two are often used as a mixture, which typically contains more trans-1,2-dichloroethene. Both cis- and trans-1,2-dichloroethene are low molecular weight organochlorides with high vapor pressures and vapor densities heavier than air (NLM 2022a, 2022b).

Table 4-1. Chemical Identity of Isomers of 1,2-Dichloroethene

Characteristic	Information[a]		
Chemical name	1,2-Dichloroethene	cis-1,2-Dichloroethene	trans-1,2-Dichloroethene
Synonym(s) and registered trade name(s)	Acetylene dichloride; 1,2-Dichloroethylene; sym-1,2-Dichloroethylene; 1,2-DCE; Dioform[b]	(Z)-1,2-Dichloroethene; (Z)-1,2-Dichloroethylene; cis-Acetylene dichloride; cis-1,2-Dichloroethylene; cis-Dichloroethylene	(E)-1,2-Dichloroethene; (E)-1,2-Dichloroethylene; trans-Acetylene dichloride; trans-1,2-Dichloroethylene; trans-Dichloroethylene
Chemical formula	$C_2H_2Cl_2$	$C_2H_2Cl_2$	$C_2H_2Cl_2$
Chemical structure			
CAS Registry Number	540-59-0	156-59-2	156-60-5

[a]All information from NLM (2022a; cis-1,2-dichloroethene) and NLM (2022b; trans-1,2-dichloroethene), except where noted.
[b]Bennett 1981.

CAS = Chemical Abstracts Services

Table 4-2. Physical and Chemical Properties of cis- and trans-1,2-Dichloroethene

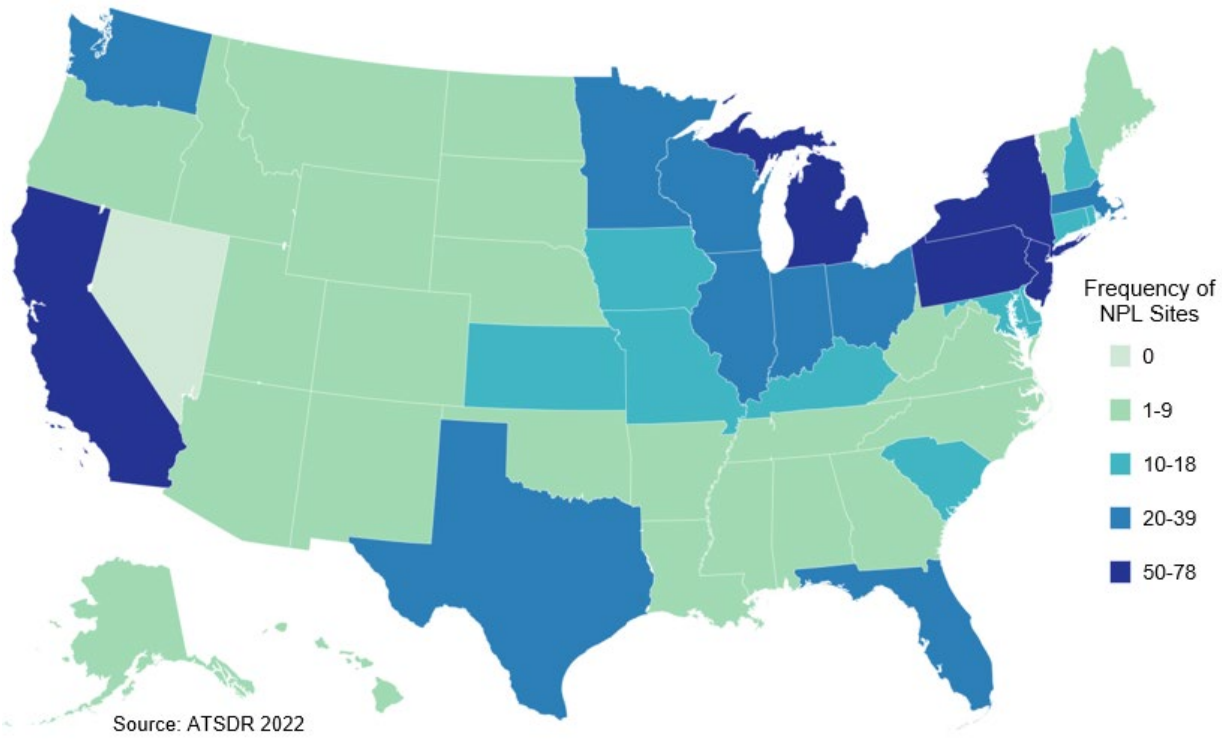
Property	cis-1,2-Dichloroethene	trans-1,2-Dichloroethene	Reference
Molecular weight	96.95	96.95	NLM 2022a, 2022b
Color	Colorless	Colorless	NLM 2022a, 2022b
Physical state	Liquid	Liquid	Hawley 1981; NLM 2022a, 2022b
Melting point	-80.0°C	-49.8°C	NLM 2022a, 2022b
Boiling point	58–60°C at 760 mmHg	47–49°C at 760 mmHg	NLM 2022a, 2022b
Density (g/cm^3)	1.2837	1.2565	NLM 2022a, 2022b
Odor	Sweetish	Sweetish	NLM 2022a, 2022b
Odor threshold:			
Water	No data	No data	
Air	No data	Odor low: 0.3357 mg/m^3; odor high 1,975.00 ppm	NLM 2022b
Solubility:			
Water (at 25°C)	1–5 mg/mL; 6,410 mg/L at 25°C	4,520 mg/L at 25°C	NLM 2022a, 2022b
Organic solvents	Soluble in ether, alcohol, benzene, acetone, chloroform	Soluble in ether, alcohol, benzene, acetone, chloroform	Weast 1983
Partition coefficients:			
Log K_{ow}	1.86	2.09 (recommended value); 2.06	NLM 2022a, 2022b
Log K_{oc}	1.69 (estimated)	1.56 (estimated)	NLM 2022a, 2022b
Vapor pressure	200 mmHg at 25°C	265 mmHg at 20°C 395 mmHg; 410 mmHg at 30°C	Stevens 1979; NLM 2022a, 2022b
Henry's law constant at 24.8°C	$4.86x10^{-3}$ atm-m^3/mol	$8.30x10^{-3}$ atm-m^3/mol	ATSDR 2022b
Autoignition temperature	460°C	460°C	NLM 2022a, 2022b
Flashpoint	2°C; 6°C;	2°C	NLM 2022a, 2022b
Flammability limits	Class IB Flammable Liquid: flash point <73°F and boiling point ≥ 100°F	Class IB Flammable Liquid: flash point <73°F and boiling point ≥ 100°F	NLM 2022a, 2022b
Conversion factors in air at 25°C	1 ppm (v/v)=3.96 mg/m^3 1 mg/m^3=0.25 ppm (v/v)	1 ppm (v/v)=3.96 mg/m^3 1 mg/m^3=0.25 ppm (v/v)	
Explosive limits	5.6–12.8% in air	9.7–12.8% in air	NLM 2022a, 2022b

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

1,2-Dichloroethene has been identified in at least 816 of the 1,868 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2022a). However, the number of sites in which 1,2-dichloroethene has been evaluated is not known. The number of sites in each state is shown in Figure 5-1. Of these sites, 810 are located within the United States, 1 is in the Virgin Islands, and 5 are in Puerto Rico (not shown).

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



- 1,2-Dichloroethene's manufacture and use as a solvent or its use as a chemical intermediate in the synthesis of other chlorinated solvents may result in exposure to both the general population and workers employed in occupations where it is produced and used.
- The general population may be exposed to 1,2-dichloroethene from inhalation of ambient air, dermal exposure, ingestion of drinking water and ingestion of food items.
- 1,2-Dichloroethene is an anaerobic degradation product of other chlorinated solvents such as trichloroethylene (TCE) and tetrachloroethylene (PCE) and can be unintentionally released in

environments that are contaminated with these substances. This may occur in contaminated subsurface soils and groundwater, which may lead to vapor intrusion of 1,2-dichloroethene into buildings or dwellings around the contaminated sites.

- 1,2-Dichlorethene is a volatile liquid and, when released, has been shown to volatilize from environmental matrices. It is degraded in the atmosphere by reaction with atmospheric oxidants such as hydroxyl radicals, ozone molecules, and nitrate radicals, with a half-life on the order of several days.

- It is unlikely to bioconcentrate in fish and other aquatic organisms but possesses high mobility in soil and may therefore leach into groundwater.

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

1,2-Dichloroethene is a compound produced by human industrial activities. It is a known byproduct of the reductive dehalogenation of other chlorinated solvents such as TCE and PCE; therefore, there will be unintentional releases of this substance from areas that are contaminated with TCE and PCE. Other sources of environmental exposure to 1,2-dichloroethene include: process and fugitive emissions from its production and use as a chemical intermediate; evaporation from wastewater streams; landfills, and solvents; emissions from combustion or heating of polyvinyl chloride and some vinyl copolymers. Most of the 1,2-dichloroethene released in the environment will eventually enter the atmosphere or groundwater, where it may be subject to further biotic or abiotic degradation processes.

5.2.1 Production

trans-1,2-Dichloroethene may be produced by direct chlorination of acetylene at 40°C and it is frequently produced as a byproduct in the chlorination of chlorinated compounds and recycled as an intermediate for the synthesis of more useful chlorinated ethylenes (EPA 2020). Another process to manufacture 1,2-dichloroethene is the thermal dehydrochlorination of 1,1,2-trichloroethane at 500°C (Dreher et al. 2012). This process produces both 1,1-dichloroethene and 1,2-dichloroethene. Production volume submissions for 2020 submitted to the EPA Chemical Data Reporting (CDR) system indicated that 1,2-dichloroethene had a production volume of 1,000,000–<20,000,000 pounds; however, more detailed facts were omitted since they were considered confidential business information (CBI) (EPA 2022a). Under the Toxic Substances Control Act (TSCA), the CDR requires manufacturers (including importers) to provide EPA with information on the production and use of chemicals like 1,2-dichloroethene in commerce. Table 5-1 summarizes information on U.S. companies that manufactured or used 1,2-dichloroethene in 2021 (TRI21 2023).

Table 5-1. Facilities that Produce, Process, or Use 1,2-Dichloroethene

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	1,000	9,999	9, 12
CA	2	1,000	99,999	7, 9
CT	1	10,000	99,999	7, 9
IL	2	1,000	999,999	7, 12
KY	1	10,000	99,999	1, 3, 6
LA	5	100	49,999,999	1, 4, 5, 13
NE	1	10,000	99,999	11, 12
OH	1	10,000	99,999	12
SC	1	100	999	12
TX	5	0	999,999	1, 2, 3, 5, 6, 12, 13, 14

[a]U.S. Postal Service state abbreviations used.
[b]Amounts on site reported by facilities in each state.
[c]Activities/Uses:

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

Source: TRI21 2023 (Data are from 2021)

5.2.2 Import/Export

Little data are available regarding import or export volumes of 1,2-dichloroethene. In the 2016 CDR submissions, one company reported the importation of a formulated product containing <1% trans-1,2-dichloroethene (EPA 2020).

5.2.3 Use

1,2-Dichloroethene is used primarily as a chemical intermediate in the synthesis of chlorinated solvents and compounds. In many applications where 1,2-dichloroethene was previously used as an extraction solvent, methylene chloride is used instead, due to its higher ability to dissolve organics and its availability (Dreher et al. 2012). No information is available about how much, if any, 1,2-dichloroethene is currently used for solvent purposes. trans-1,2-Dichloroethene is more widely used in industry than either cis-1,2-dichloroethene or the commercial mixture (EPA 2020; Gosselin et al. 1984). Other possible uses include refrigerant, pharmaceutical manufacture, artificial pearl manufacture, and extraction of fats from fish and meat (USGS 2006).

5.2.4 Disposal

No recent information regarding disposal of 1,2-dichloroethene was identified; however, current disposal methods are anticipated to be similar to those in the 1970s through the 1990s. 1,2-Dichloroethene may be released from industries in wastewater streams; however, these compounds can be removed from wastewater by air stripping (Dilling 1977; Gossett 1987; Shen 1982a). Improved wastewater treatment methods at publicly owned treatment works (POTWs) that employ air stripping processes will remove most 1,2-dichloroethene and other VOCs from final effluents and release them in air emissions (Bennett 1989). 1,2-Dichloroethene is a potential candidate for rotary kiln incineration at 820–1,600°C, with residence times of seconds for liquids and gases and longer for solids; fluidized bed incineration at 450–980°C, with residence times of seconds for liquids and gases, and longer for solids; and liquid injection incineration at 650–1,600°C, with residence times of 0.1–2 seconds (EPA 1981b). Care must be exercised to assure complete combustion to prevent the formation of phosgene. Acid scrubbers are required to control air emissions. Information regarding the amount disposed of by each method is not available.

Experiments using a vacuum-ultraviolet excimer flow-through reactor to degrade chloro-organic compounds in water have had promising results (Baum and Oppenlander 1995). After 60 minutes of irradiation at 172 nm, the level of 1,2-dichloroethene in contaminated groundwater was reduced from 25 mg/L to below the detection limit of 0.1 mg/L. After 180 minutes of irradiation, >93% of the originally organic-bound chlorine atoms were converted to inorganic chloride ions.

trans-1,2-Dichloroethene is a hazardous substance under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Releases of trans-1,2-dichloroethene more than 1,000 pounds within a 24-hour period must be reported (EPA 2011a, 2011b). Release of trans-1,2-dichloroethene in wastewater is regulated under the Clean Water Act by the National Pollutant Discharge Elimination System (NPDES). Information regarding effluent guidelines and standards for trans-1,2-dichloroethene can be found in 40 CFR 122, 40 CFR 125, 40 CFR 413.02(i), 40 CFR 414, and 40 CFR 433.11(e) (EPA 2009a, 2010a, 2010b, 2012a, 2021a).

Pursuant to RCRA Section 3004(g)(5), EPA has restricted the land disposal of trans-1,2-dichloroethene (EPA 1988b). It may be disposed on land only if prior treatment standards have been met, or if disposal

occurs in units that satisfy the statutory no-migration standard (EPA 1988b). Proper guidelines and standards are outlined in the Code of Federal Regulations (EPA 1988b).

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 42,308 pounds (~19.2 metric tons) of 1,2-dichloroethene to the atmosphere from 20 domestic manufacturing and processing facilities in 2021 accounted for about 83% of the estimated total environmental releases from facilities required to report to the TRI (TRI21 2023). These releases are summarized in Table 5-2.

Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use 1,2-Dichloroethene[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	0	0	0	0	0	0	0	0
CA	2	63	1	0	0	0	63	1	64
CT	1	1,656	0	0	0	1,496	1,656	1,496	3,152
IL	2	1,888	0	0	3	6,728	1,888	6,731	8,619

Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use 1,2-Dichloroethene[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
KY	1	128	0	0	0	0	128	0	128
LA	5	21,919	30	0	0	0	21,949	0	21,949
NE	1	15,656	0	0	0	0	15,656	0	15,656
OH	1	2	0	0	0	0	2	0	2
SC	1	1	0	0	0	0	1	0	1
TX	5	995	0	0	1	0	996	0	996
Total	20	42,308	31	0	4	8,224	42,339	8,228	50,567

[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]US Postal Service state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, wastewater treatment (metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown.
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI21 2023 (Data are from 2021)

No air emissions data for 1,2-dichloroethene were provided in the 2017 National Emissions Inventory or any time since reporting began in 2008 (EPA 2021b). In 2020, the EPA released a risk evaluation of 1,2-dichloroethene that provided some quantitative emission data; however, these data were simply derived from the 2018 TRI database (EPA 2020). This document cited potentially relevant Organisation for Economic Co-operation and Development (OECD) Emission Scenario Documents; however, a review of these documents did not contain data specifically related to 1,2-dichloroethene emissions (OECD 2011, 2015).

1,2-Dichloroethene may be released to the atmosphere in emissions from production facilities, contaminated wastewaters, contaminated waste disposal sites, and the pyrolysis and combustion of polyvinyl chloride and some vinyl copolymers. It may also be released during its use as a solvent and

extractant, in organic synthesis, and in the manufacture of perfumes, lacquers, and thermoplastics but recent quantitative data are lacking (Michal 1976; Shen 1982b).

5.3.2 Water

Estimated releases of 31 pounds (~0.014 metric tons) of 1,2-dichloroethene to surface water from 20 domestic manufacturing and processing facilities in 2021, accounted for <1% of the estimated total environmental releases from facilities required to report to the TRI (TRI21 2023). These releases are summarized in Table 5-2.

No recent information on 1,2-dichloroethene emissions to water were identified. Older studies show that 1,2-dichloroethene may be released to surface waters via surface runoff from contaminated waste disposal sites, wastewater from a variety of industrial sources, and from some POTWs. 1,2-Dichloroethene has been found in effluents from manufacturing and processing sites and from industries involved in its use as a solvent and extractant, in organic synthesis, and in the manufacture of perfumes, lacquers, and thermoplastics (Hawley 1981). As part of a comprehensive EPA survey of industrial facilities and POTWs, 4,000 samples of wastewater were analyzed. The findings indicated that cis- or trans-1,2-dichloroethene are sometimes found in wastewater from petroleum refining; coal mining; foundries; nonferrous metal manufacture; POTWs; paint and ink formulation; rubber processing; steam electricity generation; leather tanning; iron and steel manufacture; textile mills; auto and other laundries; explosives factories; and production of inorganic chemicals, mechanical products, plastics and synthetics, electrical components and electronics, pharmaceuticals, organic chemicals and plastics, and transportation equipment (EPA 1980b).

1,2-Dichloroethene is a reductive dehalogenation degradation product of TCE and PCE (cis-1,2-dichloro-ethene is most commonly the main degradation product) and, therefore, can be released to water or soil where there is contamination with these solvents (U.S. Army 2018).

In addition to spills or leachates from waste disposal sites, groundwater may be contaminated by cracked sewer interceptors carrying industrial wastes. Especially after rains, substantial loadings may leave the interceptor system through infiltration and inflow processes and enter groundwater supplies. Such phenomena have been documented in Europe (Milde et al. 1988) and similar infiltration and inflow problems are common in most older U.S. cities.

5.3.3 Soil

Estimated releases of 4 pounds (~0.002 metric tons) of 1,2-dichloroethene to soil from 20 domestic manufacturing and processing facilities in 2021, accounted for <1% of the estimated total environmental releases from facilities required to report to the TRI (TRI21 2023). No 1,2-dichloroethene was released via underground injection (TRI21 2023). These releases are summarized in Table 5-2.

Cis- and trans-1,2-dichloroethene are released to soil from the disposal of waste materials containing these compounds (Barber et al. 1988; Fain et al. 1987). They also may be formed in landfills, aquifers, or sediments as anaerobic biodegradation products of tetrachloroethene, trichloroethene, 1,1,1-trichloroethane, and 1,1,2,2-tetrachloroethane, solvents commonly found in municipal and industrial landfills (Parsons et al. 1984; Smith and Dragun 1984). In muck and sediment microcosms, tetrachloroethylene is converted to 1,2-dichloroethene with a preponderance of cis-1,2-dichloroethene (Parsons et al. 1984). cis-1,2-Dichloroethene apparently is the more common isomer found, although it may be mistakenly reported as trans-1,2-dichloroethene. Because it is a priority pollutant, trans-1,2-dichloroethene is more commonly analyzed for, and the analytical procedures used generally do not distinguish between isomers (Cline and Viste 1985). Insufficient data are available to estimate the amount of 1,2-dichloroethene released to soil.

Available information for aquatic sediments is also very limited. Some researchers feel that the subsurface behavior of 1,2-dichloroethene would be similar in groundwater, soils, and sediments (Yeh and Kastenberg 1991). Most empirical information, however, comes from groundwater remediation studies, usually involving controlled laboratory microcosm studies. For some highly polluted waterbodies, for instance the Delaware and Raritan Canal, 1,2-dichloroethene detections in the water column probably reflect extensive contamination with chlorinated toxics in the sediments (Granstrom et al. 1984). Analyzing cause-source pathways in such complicated systems can be extremely difficult.

5.4 ENVIRONMENTAL FATE

5.4.1 Transport and Partitioning

Air. Occurrence of 1,2-dichloroethene in rainwater samples (Kawamura and Kaplan 1983) indicates that this compound may be removed from the atmosphere by precipitation; however, most of the 1,2-dichloroethene so removed is likely to reenter the atmosphere by volatilization. Organics with a vapor pressure of $>10^{-4}$ mmHg should exist almost entirely in the vapor phase in the atmosphere

(Eisenreich et al. 1981). Thus, cis- and trans-1,2-dichloroethene, which have vapor pressures of 215 and 336 mmHg at 25°C, respectively (Stevens 1979), are not expected to partition from the vapor phase to particulates in the atmosphere.

Water. The dominant removal mechanism for 1,2-dichloroethene in surface waters is volatilization (EPA 1979). Henry's Law constants are 4.08×10^{-3} atm-m^3/mol at 24.8°C for cis-1,2-dichloroethene and 9.38×10^{-3} atm-m^3/mol at 24.8°C for trans-1,2-dichloroethene (Gossett 1987). Based on these values, the volatilization half-life from a model river 1 m deep, flowing 1 m/second with a wind speed of 3 m/second is estimated to be 3 hours, using the method of Thomas (1982). Dilling (1977) experimentally determined that the volatilization half-life in an open beaker containing 1 ppm of test compound at a solution depth of 6.5 cm under continuous stirring (200 rpm) was 19 minutes for cis-1,2-dichloroethene and 24 minutes for trans-1,2-dichloroethene. These values correspond to volatilization half-lives of 5.0 and 6.2 hours, respectively, from a body of water 1 m deep. trans-1,2-Dichloroethene is sufficiently volatile that 50% evaporates from water in 22 minutes when stirred at 25°C; cis-1,2-dichloroethene is similarly volatile (Dilling 1977). Experiments have shown that the degradation of trans-1,2-dichloroethene is relatively slow due to ultraviolet irradiation, unless lamps of approximately 15–20 watts are used (Gürtler et al. 1994) to allow greater relative stability of the vapor form in the environment.

In fish, bioconcentration factors (BCFs) ranging between 5 and 23 have been estimated for the 1,2-dichloroethene isomers using linear regression equations based on log K_{ow}, and water solubility data (Bysshe 1982; Horvath 1982; Lyman 1982). These estimates suggest that 1,2-dichloroethene does not bioconcentrate significantly in aquatic organisms. Based on this information, there is little potential for biomagnification within aquatic food chains.

Sediment and Soil. Soil adsorption coefficients (K_{oc}) of 32–49 were estimated for the 1,2-dichloroethene isomers using a linear regression equation based on water solubility data (Lyman 1982) and the structure-activity relationship developed by Sabljic (1984). These K_{oc} values suggest that adsorption of the 1,2-dichloroethene isomers to soil, sediment, and suspended solids in water is not a significant fate process. The presence of 1,2-dichloroethene in groundwater, especially under sandy soil (Barber et al. 1988), substantiates its leachability. The relatively low K_{oc} and high vapor pressure of 1,2-dichloroethene indicate that this compound should also readily volatilize from moist soil surfaces (Swann et al. 1983).

5.4.2 Transformation and Degradation

Air. The dominant atmospheric removal process for 1,2-dichloroethene is predicted to be reaction with photochemically generated oxygenated species (e.g., hydroxyl radicals) in the troposphere. The estimated atmospheric lifetimes for cis- and trans-1,2-dichloroethene due to this removal process are 12 and 5 days, respectively (Goodman et al. 1986). These estimates are based on experimentally determined hydroxyl reaction rate constants of 2.0×10^{-12} cm^3/molecules-second at 25°C for cis-1,2-dichloroethene and 4.5×10^{-12} cm^3/molecules-second at 25°C for trans-1,2-dichloroethene. Formyl chloride has been positively identified as a product of this reaction. Experimental data indicate that the reaction of cis- and trans-1,2-dichloroethene with ozone, nitrate radicals, or singlet oxygen in the troposphere is too slow to be environmentally significant (Atkinson and Carter 1984; Sanhueza and Heicklen 1975a, 1975b). The half-life resulting from ozone attack of the double bond is 44 days for trans-1,2-dichloroethene and 129 days for cis-1,2-dichloroethene (Tuazon et al. 1984).

The primary ultraviolet (UV) absorption band for cis-1,2-dichloroethene is at 190 nm, which extends to about 240 nm (Ausbel and Wijnen 1975). The primary ultraviolet (UV) absorption band for trans-1,2-dichloroethene also extends to about 240 nm (Dahlberg 1969). A minute amount of light is absorbed in the environmentally significant range (wavelengths >290–380 nm). However, such absorption is insufficient for direct photolysis to be a significant fate process in the atmosphere.

In polluted urban airsheds, photolytic processes are a major factor in generating free radicals. Several studies summarized in Hall et al. (1989) emphasize that 1,2-dichloroethene degradation will proceed 2–4 times faster in polluted urban air exposed to UV radiation than with “pure air” containing no free radical precursors. Tuazon et al. (1988) and Jeffers et al. (1989) provide other convenient summaries of the reaction chemistry of chloroethenes and hydroxyl radicals.

Water. There is relatively little literature dealing with 1,2-dichloroethene fate and transport in surface waters. Since 1,2-dichloroethene is appreciably volatile, the usual assumption is that 1,2-dichloroethene introduced into surface waters will volatilize to the atmosphere. Chemical hydrolysis and oxidation are probably not environmentally important fate processes for 1,2-dichloroethene (EPA 1979, 1981a, 1984). Kinetic data pertaining specifically to the abiotic degradation of the 1,2-dichloroethene isomers in the environment were not located. Direct photolysis of 1,2-dichloroethene is also not likely to be important in sunlit natural waters (EPA 1979).

When released to surface waters, 1,2-dichloroethene and other chlorinated ethenes generally resist biodegradation under aerobic conditions (Fogel et al. 1986; Mudder 1981; Mudder and Musterman 1982). However, in one study, the 1,2-dichloroethene isomers were susceptible to aerobic biodegradation. In this study (Tabak et al. 1981), settled domestic wastewater was used as the inoculum with 5 ppm each of the cis- and trans- isomers. Losses in 7 days were 54% of cis-1,2-dichloroethene and 67% of trans-1,2-dichloroethene. Losses due to volatilization over a 10-day period were 34 and 33% for cis- and trans-1,2-dichloroethene, respectively. The inoculum may have contained a facultative methanotroph capable of degrading the dichloroethenes (Fogel et al. 1986). No information was found regarding biodegradation in biological waste treatment plants.

1,2-Dichloroethene undergoes slow reductive dechlorination under anaerobic conditions (Barrio-Lage et al. 1986; Fogel et al. 1986). In one study, anoxic microcosms containing uncontaminated organic sediment and water to simulate the groundwater environment were spiked with 5 mg/L of test compound. First-order rate constants were obtained that correspond to half-lives of 88–339 and 132–147 days for cis- and trans-1,2-dichloroethene, respectively. No degradation occurred in sterile microcosms; thus, loss of the compounds was assumed to be due entirely to anaerobic biodegradation. cis-1,2-Dichloroethene degraded to chloroethane and vinyl chloride (a human carcinogen), while trans-1,2-dichloroethene degraded to vinyl chloride only (Barrio-Lage et al. 1986). When cis- and trans-1,2-dichloroethene were incubated with methanogenic aquifer material from a site near a landfill, at least 16 weeks passed before trans-1,2-dichloroethene degradation began (Wilson et al. 1986). During the same time, cis-1,2-dichloroethene was reduced to <2% of the concentration in the autoclaved control, and vinyl chloride appeared after only 1–2 weeks of incubation; therefore, cis-1,2-dichloroethene degrades more rapidly. After 40 weeks, the trans-1,2-dichloroethene concentration fell to 18% of that in the autoclaved control containing trans-1,2-dichloroethene. Trace amounts of cis-1,2-dichloroethene remained in the unsterilized microcosm beyond 40 weeks. Tandoi et al. (1994) found that an anaerobic enrichment culture, using methanol as an electron donor, rapidly metabolized cis-1,2-dichloroethene to vinyl chloride with near zero-order kinetics and apparent inhibition of subsequent vinyl chloride dechlorination. trans-1,2-Dichloroethene was converted to vinyl chloride more slowly with first-order kinetics and an estimated half-life of 9.5 hours and did not inhibit vinyl chloride dechlorination.

Hopkins and McCarty (1995) performed an evaluation of the aerobic co-metabolism of dichloroethene isomers, using phenol and toluene as the primary substrates, in a shallow aquifer at a pilot test facility. In an earlier study, a methane substrate was highly successful at transforming trans-1,2-dichloroethene in groundwater, but removal efficiency was rather low for cis-1,2-dichloroethene. Phenol was found to be

superior to methane for *in situ* degradation of cis-1,2-dichloroethene, providing up to 90% removal in one pass at concentrations up to 1 mg/L. Removal of trans-1,2-dichloroethene was 74% when phenol was used. Semprini (1995) also demonstrated in pilot scale field studies of aerobic co-metabolic transformations that indigenous microbes grown on phenol are more effective at degrading cis-1,2-dichloroethene than are microbes grown on methane.

A study was performed on a sand aquifer at an industrial site near the town of St. Joseph, Michigan, to improve the understanding of the distribution of chlorinated aliphatic hydrocarbons (CAHs) years after contamination occurred (Semprini 1995). Groundwater concentrations varied significantly with depth. Relatively high concentrations of CAHs existed at all locations within 20 m of the center of the plume. The dominant dichloroethene isomer present was cis-1,2-dichloroethene, with maximum concentrations of cis- and trans-1,2-dichloroethene of 133 and 3.9 mg/L, respectively. cis-1,2-Dichloroethene was observed in a transition zone between high and decreasing trichloroethene concentrations.

Anaerobic biotransformation by methanogenic bacteria was the earliest documented research on the biodegradation of 1,2-dichloroethene. In addition to studies in the United States (Barrio-Lage at al. 1986; Ehlke et al. 1992; Parsons et al. 1984; Silka and Wallen 1988), there has been good documentation of similar phenomena in sandy aquifers near Berlin, Germany (Kastner 1991; Leschber et al. 1990) and in groundwater supplies near a landfill in Ottawa, Canada (Lesage et al. 1990). In addition to anaerobic pathways, laboratory studies suggest that ammonia-oxidizing aerobic bacteria (Vannelli et al. 1990) and facultative sulfur-bacteria (Bagley and Gossett 1990) can biodegrade chlorinated aliphatic hydrocarbons. Burback and Perry (1993) demonstrated that 1,2-dichloroethene, when added singly to groundwater, is catabolized by *Mycobacterium vaccae*. At 100 ppm, 1,2-dichloroethene was catabolized <50%. A wide range of estimates for reaction rates and pollutant half-lives have been reported. The biodegradation processes appear to be highly site specific, and influenced by the types of bacteria present, the presence of aerobic or anaerobic conditions, the presence of other substrates such as methane or sulfide, and the toxicity impacts from the various metabolites (Janssen et al. 1988).

Sediment and Soil. Studies showing that cis- and trans-1,2-dichloroethene degrade in nonsterile groundwater microcosms (Barrio-Lage et al. 1986; Wilson et al. 1986) suggest that these compounds undergo anaerobic biodegradation in soil and that this process may be the sole mechanism by which 1,2-dichloroethene degrades in soil. Hallen et al. (1986) found that when cis- and trans-1,2-dichloro-ethene were incubated in a system inoculated with anaerobic sludge from a municipal digester to simulate anaerobic conditions in a landfill, vinyl chloride appeared within 6 weeks. Biodegradation of trans-

1,2-dichloroethene was studied in microcosms containing uncontaminated organic sediment from the Everglades and allowed to stand to ensure oxygen depletion. Under these anoxic conditions, 50% of the chemical was lost within 6 months (Barrio-Lage et al. 1986). The fact that ethyl chloride as well as vinyl chloride are produced indicates that there are different pathways in the sequential dechlorination of cis-1,2-dichloroethene. In an aerobic environment that studied several soils from an aquifer in Oklahoma, biodegradation was shown to occur quite readily with 50% disappearance over 3 weeks for cis-1,2-dichloroethene and 4 weeks for trans-1,2-dichloroethene (Klier et al. 1999). In another study, the concentration of trans-1,2-dichloroethene was determined in soil in sealed ampules to prevent volatilization; concentrations remained constant over 20 days, suggesting that biodegradation in soil may not be a major pathway for trans-1,2-dichloroethene (U.S. Army 1994).

The aerobic biodegradation of *cis*-1,2-dichloroethene was studied in groundwater mixed with sediment obtained from two sites in Denmark (Broholm et al. 2005). The results of the experiments revealed 35% removal after 274 days and 50% removal after 204 days for the two different sites; with removal being dependent on the biodegradation of vinyl chloride.

There are no transformation and degradation studies dealing with sediments. 1,2-Dichloroethene does not show significant bioconcentration or bioaccumulation tendencies and in outside groundwater, would tend to volatilize and move to the atmosphere. Some researchers feel that the behavior of 1,2-dichloroethene in sediments would be similar to patterns documented for soils or groundwater (Yeh and Kastenberg 1991).

5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to 1,2-dichloroethene depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of 1,2-dichloroethene 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 1,2-dichloroethene 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 5-3 shows the detection limits that are typically achieved by analytical analysis in environmental media.

Table 5-3. Lowest Limit of Detection for 1,2-Dichloroethene Based on Standards[a]

Media	Detection limit	Reference
Air	Generally, in the sub-ppbv in 1 L air samples using the GC/MS operated in the full SCAN mode	EPA 1996a
Drinking water	0.06 ppb	EPA 1996b
Surface water and groundwater	0.06 ppb	EPA 1996b
Soil	1 ppb	EPA 1996c
Sediment	1 ppb	EPA 1996c
Whole blood	0.010 ng/mL	CDC 2021

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

GC = gas chromatography; MS = mass spectrometry

Detections of 1,2-dichloroethene in air, water, and soil at NPL sites are summarized in Table 5-4.

Table 5-4. 1,2-Dichloroethene, cis-1,2-Dichloroethene, and trans-1,2-Dichloroethene 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
1,2-Dichloroethene					
Water (ppb)	91	107	18.6	312	179
Soil (ppb)	750	799	82.0	69	53
Air (ppbv)	1.25	2.46	21.5	15	11
cis-1,2-Dichloroethene					
Water (ppb)	37.7	46.2	23.3	192	117
Soil (ppb)	1,900	1,380	67.9	17	15
Air (ppbv)	1.81	4.92	37.2	21	18
trans-1,2-Dichloroethene					
Water (ppb)	126	165	20.0	356	212
Soil (ppb)	707	1,240	66.0	62	56
Air (ppbv)	1.00	1.95	19.4	17	15

[a]Concentrations found in ATSDR site documents from 1981 to 2022 for 1,868 NPL sites (ATSDR 2022a). 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

1,2-Dichloroethene is a pollutant monitored in the national Air Quality System (AQS) database which contains ambient air pollution data collected by EPA, state, local, and tribal air pollution control agencies from thousands of monitoring stations throughout the country. Table 5-5 shows the range of yearly mean 24-hour concentrations and maximum concentrations measured of cis-1,2-dichloroethene at monitoring stations across the United States from 2016 to 2021.

Table 5-5. Summary of Annual Concentration of cis-1,2-Dichloroethene (ppbv) Measured in Ambient Air at Locations Across the United States[a]

Year	Number of samples	Range of arithmetic mean at all locations	Maximum concentration
2016	6,722	ND–0.0485	0.89
2017	6,659	ND–0.0833	0.98
2018	6,477	ND–0.594	8.80
2019	4,856	ND–0.083	4.05
2020	4,197	ND–0.034	0.82
2021	6,152	ND–0.073	1.29

[a]Values were originally reported in parts per billion carbon (ppbC) and converted to ppbv; 24-hour sampling period.

Source: EPA (2022b)

Pratt et al. (2000) reported the results of ambient air monitoring collected at 25 sites throughout the state of Minnesota over an 8-year period (1991–1998). The mean and maximum concentration of 1,2-dichloroethene in 3,650 samples (119 positive detections) were 0.02 and 2.18 $\mu g/m^3$ (0.005 and 0.550 ppbv), respectively. Levels of 1,2-dichloroethene were monitored near a residential area around a large-scale petrochemical complex in central Taiwan (Hsu et al 2018). A relatively higher concentration was observed during the summer as compared to the spring and winter months, but the levels did not vary greatly depending upon the distance of the sampling location (<5 or 10–50 km away from the complex) with mean levels ranging from 0.010 to 0.091 ppbv.

Historical air monitoring data from the 1970s and 1980s is shown in Table 5-6. Maximum 1,2-dichloroethene concentrations were detected in landfill gas and ranged from 3,260 ppbv (Vogt and Walsh 1985) in a municipal landfill simulator to 75,600 ppbv at two Long Island landfills (Lipsky and Jacot 1985).

Table 5-6. Historical Air Monitoring Data for 1,2-Dichloroethene in the United States

Media	Location	Sampling date	Isomer	Concentration (ppbv)	Comments	Reference
Ambient air	Houston, Texas		cis	0.071 (mean)	General urban atmosphere	EPA 1983a
	St. Louis, Missouri	May 1980		0.039 (mean		
	Denver, Colorado	May–June 1980		0.076 (mean)		
	Riverside, California	June 1980		0.060 mean)		
	Staten Island, New York	July 1980		0.018 (mean)		
	Pittsburgh, Pennsylvania	March–April 1981		0.013 (mean)		
	Chicago, Illinois	April–May 1981		0.019 (mean)		
	Edison, New Jersey	NS	NS	1.3 (maximum)	Kin-Buc disposal site	EPA 1978
	Tulsa, Oklahoma	NS	NS	<0.1		EPA 1978
	Kanawha Valley, West Virginia			0.08		
	Front Royal, Virginia			0.1		
	South Charleston, West Virginia			<0.08		
	Birmingham, Alabama			<0.1		
	Baton Rouge, Louisiana			<0.1		
	Upland, California			<0.1		
	Magna, Vermont			0.08		
	Grand Canyon, Arizona			0.065		
	Geismar, Louisiana			2.6 (maximum)		
	Niagara Falls, New York	1978	NS	Trace	Detected in air outside three homes in Old Love Canal hazardous waste site (detection limit not stated)	Barkley et al. 1980
	New Jersey	NS	NS	NS	Four NPL sites and one municipal landfill; detected in air samples collected at three of five sites; occurred in 75–100% of samples collected at these sites (detection limit ≥0.1 ppb)	LaRegina et al. 1986

Table 5-6. Historical Air Monitoring Data for 1,2-Dichloroethene in the United States

Media	Location	Sampling date	Isomer	Concentration (ppbv)	Comments	Reference
	Edison, New Jersey	NS	trans	0.093		Brodzinsky and Singh 1982
	Urban/suburban (669 sites)	NS	cis	0.068 (median)		
				3.5 (maximum)		
	Source areas (101 sites)	NS	cis	0.3 (median)		
				6.7 (maximum)		
	Pullman, Washington (rural area)	December 1974–February 1975	NS	ND	Detection limit 5 ppt	Grimsrud and Rasmussen 1975
Indoor air	Niagara Falls, New York	1978	NS	0.015	Air in basement of a home in Old Love Canal	Barkley et al. 1980
Landfill gas	Selected U.S. landfills	NS	NS	70 (mean)	Secondary source	Vogt and Walsh 1985
				3,600 (maximum)		
	Municipal landfill simulator	February 1983–February 1984	NS	210 (mean)	Simulation	Vogt and Walsh 1985
				3,260 (maximum)		
	Long Island, New York	NS	trans	75,600 (maximum)	Air samples collected from methane vents at two sanitary landfills	Lipsky and Jacot 1985
	California	NS	trans	59,000 (maximum)	20 class II landfills	Wood and Porter 1987

ND = not detected; NPL = National Priorities List; NS = not stated

A predecessor to the AQS system was the National Ambient Database, which compiled indoor and outdoor air monitoring data on VOCs in the United States (Shah and Singh 1988). Based on information from 161 data points collected in the 1980s, outdoor 1,2-dichloroethene daily ambient air concentrations averaged 0.326 ppbv, with a median of 0.037 ppbv and with 75% of the values falling below a concentration of 0.113 ppbv.

5.5.2 Water

1,2-Dichloroethene has been detected in surface water, groundwater, and drinking water, as well as in industrial and municipal effluents, urban runoff, and leachate from landfills throughout the United States. Table 5-7 summarizes some monitoring data for 1,2-dichloroethene in these media. In some of the studies, only one of the 1,2-dichloroethene isomers was monitored; in several of the studies, the authors did not mention the specific isomer monitored. 1,2-Dichloroethene is often found in the groundwater at Superfund sites along with other halogenated organic compounds, such as 1,2-dibromoethane, vinyl chloride, 1,1,2,2-tetrachloroethane, 1,1,2-trichloroethane, trichloroethene, and tetrachloroethene (ATSDR 2019; EPA 2012b).

The 1996 Safe Drinking Water Act (SDWA) amendments require that, once every 5 years, EPA issue a new list of no more than 30 unregulated contaminants to be monitored by public water systems (PWSs). 1,2-Dichloroethene was tested for in the first two rounds of the Unregulated Contaminant Monitoring Rule (UCMR). A total of 16,705 PWS were tested for cis-1,2-dichloroethene and 19,945 PWS were tested for trans-1,2-dichloroethene (EPA 2001). A total of 1.47% of the systems tested had at least one positive detection for cis-1,2-dichloroethene and 0.64% of the systems having at least one positive detection for trans-1,2-dichloroethene. The Maximum Contaminant Level (MCL) was reported as 70 µg/L (cis-1,2-dichloroethene) and 100 µg/L (trans-1,2-dichloroethene). It was reported that 0.03% of the systems had a level greater than the MCL for the cis-1,2-dichloroethene and 0.01% of the systems had a level that exceeded the MCL for trans-1,2-dichloroethene. The maximum level of cis-1,2-dichloroethene was 213 µg/L for a system in the state of Ohio and the maximum level of trans-1,2-dichloroethene was 190 µg/L for a system in California. In a four-city study (Cincinnati, Ohio; St. Louis, Missouri; Atlanta, Georgia; Hartford, Connecticut) to determine the major source type of priority pollutants in tap water and POTW influents, it was found that 43, 38, and 28% of commercial sources, industrial sources, and POTW influents, respectively, contained trans-1,2-dichloroethene (EPA 1981c).

Table 5-7. Water Monitoring Data for 1,2-Dichloroethene

Media	Location	Sampling date	Isomer	Concentration (ppb)	Comments	Reference
Surface water	Hylebos Waterway in the Puget Sound	1979	NS	0.8–2.4		NOAA 1980
	Potomac River in Quantico, Virginia	Spring 1986	trans	<2	One sample analyzed (detection limit not reported)	Hall et al. 1987
	12 sites in the Delaware and Raritan Canal in New Jersey	August 1979–January 1980	NS	ND	Detection limit not reported	Granstrom et al. 1984
	Indian River in Vero Beach, Florida	May 1981–May 1982	NS	ND	13 samples (detection limit 4.0 µg/L)	Wang et al. 1985b
	Drainage canal discharging into the Indian River in Vero Beach, Florida	May 1981–May 1982	NS	4.0–48.1; 15.7 (mean)	Canal receiving contaminated groundwater; detected in 23 of 39 samples (detection limit 4.0 µg/L)	Wang et al. 1985b
	New Jersey	1977–1979	trans	1,307.5 (maximum)	Detected in 172 of 273 samples (detection limit not reported)	Page 1981
	Wilson Creek (adjacent to hazardous waste site) in Bullitt County, Kentucky	February 1979	NS	75 (maximum)		Stonebraker and Smith 1980
Ground-water	178 CERCLA sites	1981–1984	trans	NS	Frequency of detection 29/1%	Plumb 1987
	3,498 aquifer samples from around the United States	NS	trans	100 (maximum)		USGS 2006
	New Jersey	1977–1979	trans	818.6 (maximum)	Detected in 193 of 378 samples	Page 1981
	Fort Bragg, NC	October 2017	cis	19.4 – 65.6		U.S. Army 2018
	Camp Lejeune, NC	1985-1995	cis and trans	>6,000 (maximum)	Multiple groundwater wells monitored throughout the site for 1,2-dichloroethene produced as a degradation product of TCE and PCE	ATSDR 2010

Table 5-7. Water Monitoring Data for 1,2-Dichloroethene

Media	Location	Sampling date	Isomer	Concentration (ppb)	Comments	Reference
	Colorado	1993	cis	6.1 (maximum)		Bruce and McMahon 1996
	208 wells located in urban areas in the United States	NS	cis	82 (maximum)		Kolpin et al 1997
	Wisconsin	Sampling results as of June 30, 1984	NS	NS	Detected in 5 of 1,174 community wells and 12 of 617 private wells (detection limit 1.0–5.0 µg/L)	Krill and Sonzogni 1986
	Wausau, Wisconsin	NS	cis	83.3	Raw well water	Hand et al. 1986
	Wisconsin	1985–1987	NS	3,900 (maximum)	Detected at 5 of 26 sites	Wisconsin DNR 1988
	Montgomery County, Missouri	1983	trans	27–320; 158 (mean)	Detected in four samples	Dever 1986
	Potomac-Raritan-Magothy aquifer system (adjacent to the Delaware River)	1980–1982	trans	NS	Detected in 12 of 179 wells in the outcrop area and not detected in 115 wells in the downdip of the outcrop (detection limit 1 µg/L)	Fusillo et al. 1985
	Nebraska	Summer 1982	NS	2.1 (maximum); 0.50 (median)	Detected in 3 of 63 samples (detection limit 0.2 µg/L); private wells	Goodenkauf and Atkinson 1986
	Nebraska	1983–1984	NS	2.9	Detected in 1 of 97 samples; sources for public water system	Goodenkauf and Atkinson 1986
	Western Connecticut manufacturing plant	NS	trans	1.2–320.9	Detected in seven of nine monitoring wells	DOI 1983
	Biscayne aquifer, Miami, Florida	November 1982 and March 1983	trans	0.25–28 (range of average concentration from the mix areas)	12 total samples from six geographical areas defined within the study area	Singh and Organ 198

Table 5-7. Water Monitoring Data for 1,2-Dichloroethene

Media	Location	Sampling date	Isomer	Concentration (ppb)	Comments	Reference
	Miami Drum Services in Miami, Florida	1981	cis	839 (maximum)	Hazardous waste site	Myers 1983
	Biscayne aquifer in vicinity of Miami Drum Site	1983	NS	19 (mean)	Detected in two of three samples (detection limit not reported)	Myers 1983
	Piper Aircraft Corporation in Vero Beach, Florida	April 19811983–December 1983	NS	1,000–4,000	At site of a leaking subsurface trichloroethylene storage tank	Wang et al. 1985a
	Lakewood, Washington	December 1983	trans	250–435; 330 (mean)	Detected in 11 of 11 samples; in the vicinity of an NPL site	Wolf and Gorelik 1984
	Western Processing, Kings Country, Washington	November 1982	trans	Qualitatively identified	Hazardous waste site	Aldis et al. 1983
	Marshall landfill in Boulder County, Colorado	NS	trans	530 (onsite); 66 (offsite)	NPL site	EPA 1986a
	Minnesota	NS	cis	0.5–20,000	Detected in contaminated groundwater from 7 of 13 sites	Sabel and Clark 1984
			trans	0.6–98	Detected in contaminated groundwater from 3 of 13 sites	
	Forest Waste Disposal Site in Otisville, Michigan	NS	trans	100 (maximum)	NPL site	EPA 1986b
	Lang Property site in Pemberton Township, New Jersey	NS	trans	943 (mean); 2,500 (maximum)	NPL site	EPA 1987a
	Vega Alta Public Supply Wells in Puerto Rico	NS	NS	74 (maximum)	NPL site; detected in 89 of 168 samples (detection limit not reported)	EPA 1988a
	Ponders Corner in Pierce County, Washington	1984–1985	trans	85 (maximum)	NPL site	EPA 1986c
	Hollinsworth Solderless Terminal Co. in Fort Lauderdale, Florida	1983	NS	2,160 (maximum)	NPL site; level of dichloroethene (there was no indication whether this was 1,1- or 1,2-dichloroethene)	EPA 1986d

Table 5-7. Water Monitoring Data for 1,2-Dichloroethene

Media	Location	Sampling date	Isomer	Concentration (ppb)	Comments	Reference
	Lake wood Utility District near Tacoma, Washington	NS	trans	200	Production wells near a commercial facility	Boateng et al. 1984
Drinking water public wells	United States	1999-2002	Cis and trans	0.02-1.0 (cis); 0.02-10.0 trans	Detection frequency of 1-5%	USGS 2006
Drinking water (using ground-water sources)	United States	NS	NS	2.0 (maximum)	Detected in samples collected from 16 of 466 randomly selected sites using groundwater as a raw water source (detection limit 0.2 µg/L)	Westrick et al. 1984
Drinking water	Miami, Florida	NS	trans	1		EPA 198d
Drinking water	United States	1988 to 1992; 1993 to 1997	cis and trans	213 cis; 190 trans (maximums)		EPA 2001
Drinking water (private wells)	Winnebago County, Illinois	NS	trans	ND–64; 8 (median)	Five homes tested	Illinois ENR 1984
	Philadelphia, Pennsylvania	February 1975–January 1977	NS	NS	Detected in 1 of 17 samples (detection limit not reported)	Suffet et al. 1980
	Five U.S. cities	1975	cis and trans	NS	EPA National Organics Reconnaissance Survey; cis-1,2-dichloroethene positively identified in samples from Miami, Florida; Philadelphia, Pennsylvania; and Cincinnati, Ohio; trans-1,2-dichloroethene positively identified in samples from Miami, Florida	EPA 1975

Table 5-7. Water Monitoring Data for 1,2-Dichloroethene

Media	Location	Sampling date	Isomer	Concentration (ppb)	Comments	Reference
Raw and treated drinking water	10 potable water treatment plants in Canada	July 1982–July 1983	NS	trace	Positively identified in three raw and three treated water samples (detection limit not reported)	Otson 1987
Leachate	30 potable water treatment plants in Canada	August 1979–December 1979	NS	Raw water: 23 (maximum); treated water: 32 (maximum)	Positively identified in 2 raw and 11 treated water samples	Otson et al. 1982
	NS (landfill containing mixed industrial waste)	NS	trans	45–800 (average concentration of leachates)	Detected in two of eight leachates (detection limit not reported)	Ghassemi et al. 1984
	Minnesota	NS	cis	1.4–470	Detected in leachate from five of six sites (detection limit not reported)	Sabel and Clark 1984
			trans	3.8–88	Detected in leachate from three of six sites (detection limit not reported)	Sabel and Clark 1984
	Lyon, Minnesota, municipal landfill	NS	trans	3.8 (mean)		Brown and Donnelly 1988
	Meeker, Minnesota, municipal landfill	NS	cis	190 (mean)		Brown and Donnelly 1988
			trans	170 (mean)		
	Rochester, Minnesota, municipal landfill	NS	cis	470 (mean)		Brown and Donnelly 1988
			trans	88 (mean)		
	Wisconsin, 20 municipal and industrial landfills	1985–1987	NS	310	Detected in leachate from 8 of 26 sites	Wisconsin DNR 1988
Aqueous lagoon	Forest Waste Disposal site in Otisville, Michigan	NS	trans	50	NPL site; estimate level (compound detected below quantification limit)	EPA 1986b

Table 5-7. Water Monitoring Data for 1,2-Dichloroethene

Media	Location	Sampling date	Isomer	Concentration (ppb)	Comments	Reference
Urban storm water runoff	15 U.S. cities	As of July 1982	trans	1–3 (in positive samples)	Detected in runoff from Little Rock, Arkansas and Eugene, Oregon	Cole et al. 1984
Waste-water	Los Angeles, California	NS	NS	5.2 (mean)	Effluent from a county sewage treatment plant	Gossett et al. 1983
	NS	1980/1981	Trans	Untreated: 52–60; effluent: 31–43	Municipal sewage treatment plant; detected in five of five samples	Lao et al. 1982
	Chicago, Illinois	NS	Trans	<50	Effluent from a municipal sewage treatment plant	Lue-Hing et al. 1981
	NS	NS	Trans	20 (maximum)	Treated effluent from a petroleum refinery	Snider and Manning 1982
	Owensboro, Kentucky	August 1975	Cis	NS	Chemical plant effluent	EPA 1976
	Calvert City, Kentucky	October 1975	Cis	NS	Chemical plant effluent	EPA 1976
					Industry:	
	United States	NS	trans	10 (maximum)	Coal mining	EPA 1980a
			trans	46 (maximum)	Electrical electronic components	
			trans	10 (maximum)	Foundries	
			trans	10 (maximum)	Pharmaceutical manufacturing	
			trans	75 (maximum)	Nonferrous metals manufacturing	
			trans	12 (mean)	Organic chemicals and plastics manufacturing	
			trans	190 (maximum)	Paint and ink formulation	
			trans	<10 (maximum)	Petroleum refining	
			trans	290 (maximum)	Rubber processing	

Table 5-7. Water Monitoring Data for 1,2-Dichloroethene

Media	Location	Sampling date	Isomer	Concentration (ppb)	Comments	Reference
	NS	NS	trans	260 (mean); 1,700 (maximum)	Metal finishing	EPA 1980b
			trans	2,200 (maximum)	Photographic equipment/ supplies	
			trans	75 (mean); 260 (maximum)	Nonferrous metal manufacturing	
			trans	150 (mean); 290 (maximum)	Rubber processing	
Rain-water	UCLA campus, Los Angeles, California	March 26, 1982	NS	0.230	One sample	Kawamura and Kaplan 1983

CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; EPA = Environmental Protection Agency; ND = not detected; NPL = National Priorities List; NS = not stated; POTW = public owned treatment works; UCLA = University of California at Los Angeles

In a survey of 3,498 aquifer samples from around the United States; trans-1,2-dichloroethene was detected in 0.74% of samples with levels as low as 0.2 ppb and levels as high as 100 ppb (µg/L) (USGS 2006). Older water sampling studies detected 1,2-dichloroethene in groundwater in several states and U.S. territories including Colorado, Connecticut, Florida, Maryland, Michigan, Nebraska, New Jersey, Pennsylvania, Puerto Rico, Washington, and Wisconsin (Table 5-7). In a survey of shallow groundwater from 208 wells located in urban areas in the United States, cis-1,2-dichloroethene was detected in 5.3% of wells with a maximum concentration 82 ppb (µg/L) (Kolpin et al. 1997). A survey of 2,721 drinking water wells in California, detected 1,2-dichloroethene (isomers not distinguished) in 36 wells, with a maximum contamination level of 10 ppb (µg/L) (Lam et al. 1994). A survey of chemical quality of groundwater in the unconsolidated alluvial aquifer beneath Denver Colorado was performed in 1993, which detected cis-1,2-dichloroethene in 20% of samples with a high of 6.1 ppb (µg/L) (Bruce and McMahon 1996). Concentrations of 1,2-dichloroethene isomers detected in groundwater ranged from 0.25 to 0.28 ppb (µg/L) (range of average concentrations) in six areas near Miami, Florida (Singh and Orban 1987). Groundwater contamination has been reported at numerous waste disposal sites in the United States. In a detailed study, the Wisconsin Department of Natural Resources sampled groundwater at 20 municipal and 6 industrial landfills in Wisconsin. 1,2-Dichloroethene was detected in samples from 5 of 26 landfills at a maximum concentration of 3,900 ppb (µg/L), and in leachate from 8 of 26 landfills at a maximum concentration of 310 ppb (µg/L) (Wisconsin DNR 1988).

Since 1,2-dichloroethene can be produced from biodegradation of a variety of VOCs, screening tests for VOCs or tests for such widely used solvents as TCE or PCE can provide useful screening tools for follow-up testing for 1,2-dichloroethene. For instance, a study of 19 landfill sites in Wisconsin showed that while the incidence of 1,2-dichloroethene in all test wells was 19%, approximately two-thirds of the wells showing detectable VOCs also showed detectable 1,2-dichloroethene (Wisconsin DNR 1989). In a study of a western Connecticut manufacturing plant that used large quantities of high-quality trichloroethylene for degreasing, it was found that seven of nine monitoring wells contained 1.2–320.9 ppb (µg/L) of trans-1,2-dichloroethene (DOI 1983). More localized problems from leaking underground storage tanks or chemical spills may also show up in screens for VOCs (Stenzel and Gupta 1985). Where pollution levels are not excessive, remediation or permanent treatment technologies involving combinations of granular activated carbon or air stripping can remove over 96% of VOCs such as cis-1,2-dichloroethene (Clark et al. 1988; Lee et al. 1988; Stenzel and Gupta 1985). Cis- and trans-1,2-dichloroethene are contaminants in groundwater at Camp Lejeune, North Carolina due to high levels of TCE and PCE that were released to groundwater from a dry-cleaning facility (ATSDR 2010).

Monitoring studies that have occurred since the 1980s show typical concentrations in the low ppb range; however, some sampling wells have had levels of several thousand ppb.

5.5.3 Sediment and Soil

Since 1,2-dichloroethene is volatile, soil and sediment monitoring data are typically limited to those obtained through hazardous waste site monitoring (Aldis et al. 1983; ATSDR 2019; EPA 1986c, 1987a). A soil sample collected from a monitoring location in Camp Lejeune, North Carolina had a cis-1,2-dichloroethene level of 21 µg/kg (ATSDR 2010). Soil gas pollutants in a shallow, unconfined aquifer receiving wastewater from metal-plating operations at Picatinny Arsenal in Morris County, New Jersey were found to have a maximum cis-1,2-dichloroethene concentration of 33 ppb in the vadose zone (Smith 1988).

Sediment samples from Wallace Creek at Camp Lejeune, North Carolina had total 1,2-dichloroethene levels of 31 µg/kg (ATSDR 2010). In the early 1980s, 1,2-dichloroethene was found at a concentration of >5 ppb (wet weight) in sediment at 4% of 361 stations reported in EPA's STOrage and RETrieval (STORET) database (Staples et al. 1985). No further summary information was located on the occurrence of 1,2-dichloroethene in sediments.

5.5.4 Other Media

trans-1,2-Dichloroethene concentrations ranging from 22 to 55 g/L have been detected in municipal sludge from various treatment plants throughout the United States (Feiler et al. 1980; Naylor and Loehr 1982). Few reports exist of 1,2-dichloroethene in biota from U.S. waters. This is because 1,2-dichloroethene is not a typical biota contaminant (Staples et al. 1985). Nicola et al. (1987) reported mean and maximum 1,2-dichloroethene levels of 0.04 and 0.05 ppm, respectively, in fish tissue from Commencement Bay in Tacoma, Washington. No fish obtained at the 95 stations in EPA's STORET database contained detectable levels of 1,2-dichloroethene (Staples et al. 1985).

The results of the U.S. Food and Drug Administration's (FDA) Total Diet Study for 1,2-dichloroethene (trans) from 1991–2002 and 2003–2017are shown in Table 5-8. For these studies, the FDA purchases samples of food at retail outlets throughout the United States and prepares the foods as they would be consumed and analyzes them for certain compounds.

Table 5-8. Levels of trans-1,2-Dichloroethene in FDA Total Diet Studies[a]

Year	Food item	Concentration (ppb)
1998	Cheddar cheese	10
1999	Cheddar cheese	24
2000	Cheddar cheese	16
	Cheddar cheese	42
2001	Frankfurters, beef, boiled	11
	Frankfurters, beef, boiled	2
	Cheddar cheese	13
	Cheddar cheese	14
	Swiss cheese	2
	Chicken, fried (breast, leg, and thigh), fast-food	2
2002	Cheddar cheese	6
	Cheddar cheese	19
	Cheddar cheese	11
	Meatloaf, homemade	2
	Margarine, stick, regular (salted)	2
	Butter, regular	2
2003	Cheese, cheddar, natural (sharp/mild)	13

[a]There were no detections in years 1991–1997 or 2004–2017.

Source: FDA 2022a

5.6 GENERAL POPULATION EXPOSURE

The general population may be exposed to 1,2-dichloroethene in urban air and drinking water, with higher possibilities of exposure in community systems relying on groundwater supplies. Contaminated tap water can cause exposure via ingestion, inhalation, and dermal contact during showering, bathing, cooking, and laundering clothing. Inhalation is the most probable route of exposure. EPA used urban air estimated concentrations of 1,2-dichloroethene of 0.013–0.076 ppbv (0.052–0.30 µg/m^3) and based on this concentration range, exposure levels correspond to an average daily intake of 1–6 µg 1,2-dichloroethene, assuming an average daily intake of 20 m^3 of air (EPA 1983b).

1,2-Dichloroethene in water is expected to rapidly volatilize; thus, there is potential for inhalation exposure during showering, bathing, cooking, and laundering clothing. ATSDR's three-compartment Shower and Household-Use Exposure (SHOWER) model predicts air concentrations in the shower stall, bathroom, and main house throughout the day by estimating the contribution from showering or bathing and the contribution from other water sources in the house, such as the dishwasher, clothes washer, and

faucets. This information along with human activity patterns are used to calculate a daily time-weighted average exposure concentration via inhalation exposure and from dermal uptake from skin contact. ATSDR's SHOWER model is available by sending a request to showermodel@cdc.gov. For a 15-minute exposure time, the SHOWER model predicts 63% exposure from showering, 35% from usage of the main house, and 2% from bathroom use after showering (ATSDR 2022b).

Vapor intrusion into indoor air may also be a potential source of 1,2-dichloroethene exposure, as vapor intrusion has been observed for several VOCs with similar properties. EPA has reported that 1,2-dichloroethene is rarely detected in indoor air; however, when it is detected, it most likely occurs because of vapor intrusion from contaminated groundwater or subsurface soil (EPA 2015). A review of vapor intrusion data from 148 ATSDR public health assessments completed between 1994 and 2009 identified 14 sites with detected concentrations of dichloroethene in groundwater, soil gas, or air (Burk and Zarus 2013). Indoor air was sampled at nine of the sites with dichloroethene and detected at levels of 0.08–55 ppb, which is below ATSDR's acute-duration inhalation MRL. Dichloroethene was detected in groundwater at 12 of the sites ranging from 0.33 to 6,500 µg/L, and none of the sites had dichloroethene groundwater concentrations at levels of concern from vapor intrusion based on the acute MRL and assuming attenuation of concentrations by a factor of 1,000 as the soil gas moves from the groundwater to indoor air.

Brenner (2010) studied four large buildings at the National Aeronautics and Space Administration (NASA) Ames Research Center in Moffett Field, California and determined that the presence of cis-1,2-dichloroethene in indoor air samples arose due to contamination of groundwater with TCE and the subsequent degradation to 1,2-dichloroethene followed by vapor intrusion into the buildings. The Michigan Department of Health in consultation with ATSDR performed a vapor intrusion assessment of a chlorinated solvent groundwater plume that had migrated from a former General Motors facility under a residential neighborhood in Livonia (Wayne County), Michigan (ATSDR 2012). Ten residences were tested, and cis-1,2-dichloroethene was detected in soil gas at two locations while trans-1,2-dichloroethene was detected at five locations. There were detections of trans-1,2-dichloroethene in the soil gas at two properties that exceeded the air screening level of 630 µg/m^3. The two homes which exceeded the soil gas screening level for trans-1,2-dichloroethene, had levels of 1,300 and 70,000 µg/m^3. Analyzing the data further, the Michigan Department of Health and the EPA could not determine if vapor intrusion was the source of these anomalously high levels as previous sampling studies showed low or no detections in these residences.

Ashley et al. (1994) determined the internal dose of 32 VOCs in 600 or more people in the United States who participated in the Third National Health and Nutrition Examination Survey (NHANES III). Detectable concentrations of cis- and trans-1,2-dichloroethene were found in <10% of the blood samples examined. Their detection limits were 0.013 and 0.014 ppb, respectively. The most recent NHANES data compiled for 1,2-dichloroethene from the 2011–2012 sampling period reported that 1,2-dichloroethene (both cis- and trans- isomers) blood levels were below the detection limit of 0.010 ng/mL for all age and demographic groups studied (CDC 2021).

No specific data were reported for 1,2-dichloroethene; however, certain cooking practices release VOCs to air so inhalation exposures could result for occupations such as chefs or other workers in restaurant settings (Wang et al. 2018). It was reported that VOCs such as 1,2-dichloroethene are emitted from additive manufacturing and 3D printing machines (Zisook et al. 2020); therefore, workers in these emerging technologies could be occupationally exposed to 1,2-dichloroethene.

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Other than individuals who are occupationally exposed, populations with potentially high exposure include those living near production and processing facilities, hazardous waste sites, municipal wastewater treatment plants, and municipal landfills. Near production and processing facilities, certain hazardous waste sites, and municipal landfills, potential exists for exposure to elevated levels of 1,2-dichloroethene in air downwind of the sites and in contaminated drinking water from groundwater downgradient of the sites. Sites that are contaminated with TCE and PCE can have high levels of 1,2-dichloroethene since this is a degradation product of these substances. As an example, people stationed and living at Camp Lejeune, North Carolina were potentially exposed to high levels of 1,2-dichloroethene in the water supply due to high levels of TCE and PCE that were released from a dry-cleaning facility that operated from 1964 until 2005 (ATSDR 2010).

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 1,2-dichloroethene 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 1,2-dichloroethene.

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 1,2-dichloroethene that are discussed in Chapter 2 are summarized in Figures 6-1, 6-2, and 6-3. The purpose of this figure is to illustrate the information concerning the health effects of 1,2-dichloroethene. 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. Note that some studies evaluated multiple endpoints.

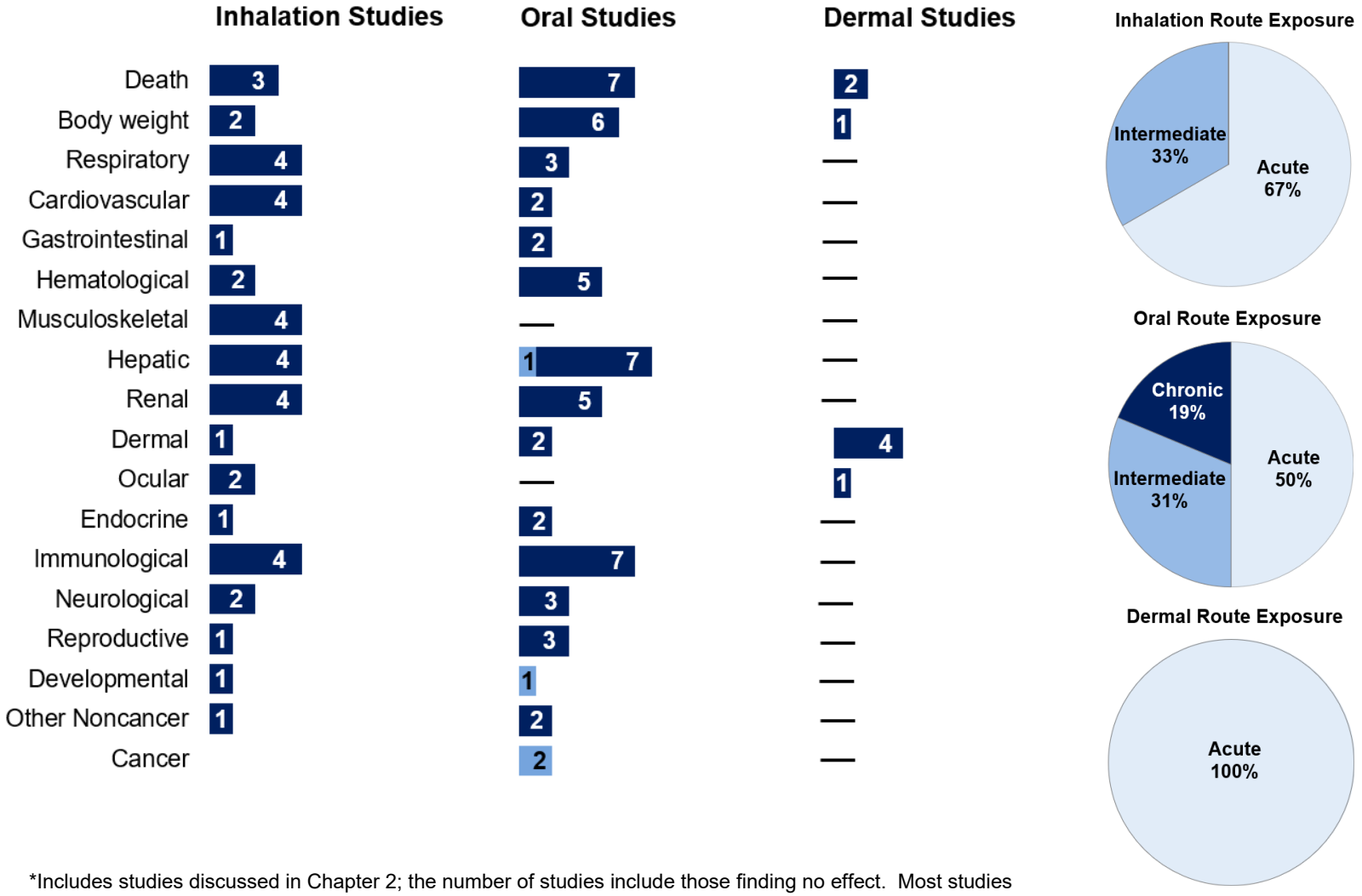
6.2 Identification of Data Needs

Missing information in Figures 6-1, 6-2, and 6-3 should not be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Figure 6-1. Summary of Existing Health Effects Studies on trans-1,2-Dichloroethene by Route and Endpoint*

Lethality and potential hepatic and immune effects were the most studied endpoints for trans-1,2-dichoroethene

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

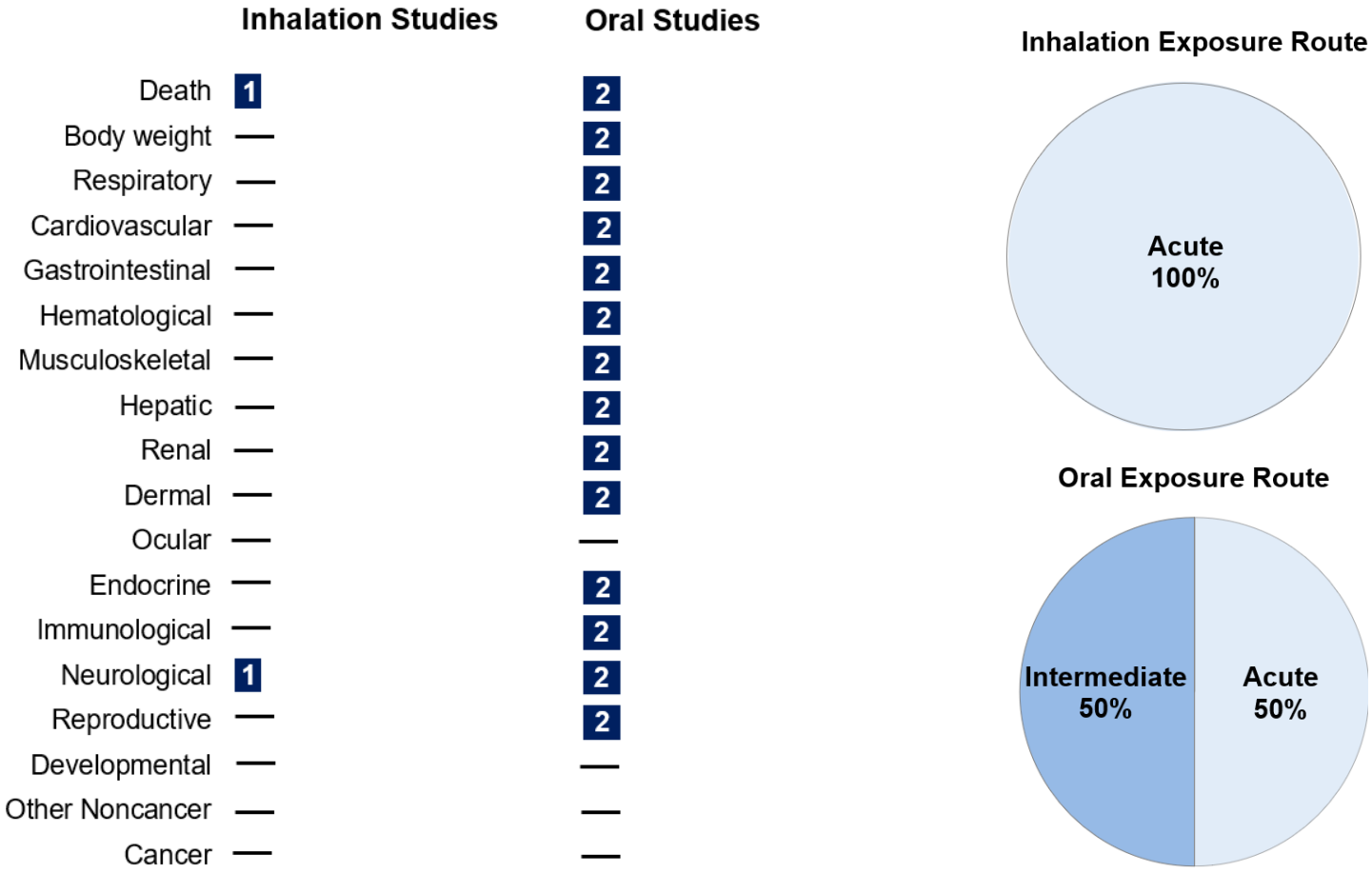


*Includes studies discussed in Chapter 2; the number of studies include those finding no effect. Most studies examined multiple endpoints.

Figure 6-2. Summary of Existing Health Effects Studies on cis-1,2-Dichloroethene by Route and Endpoint*

Lethality and neurological effects were the most studied endpoints for cis-1,2-dichloroethene

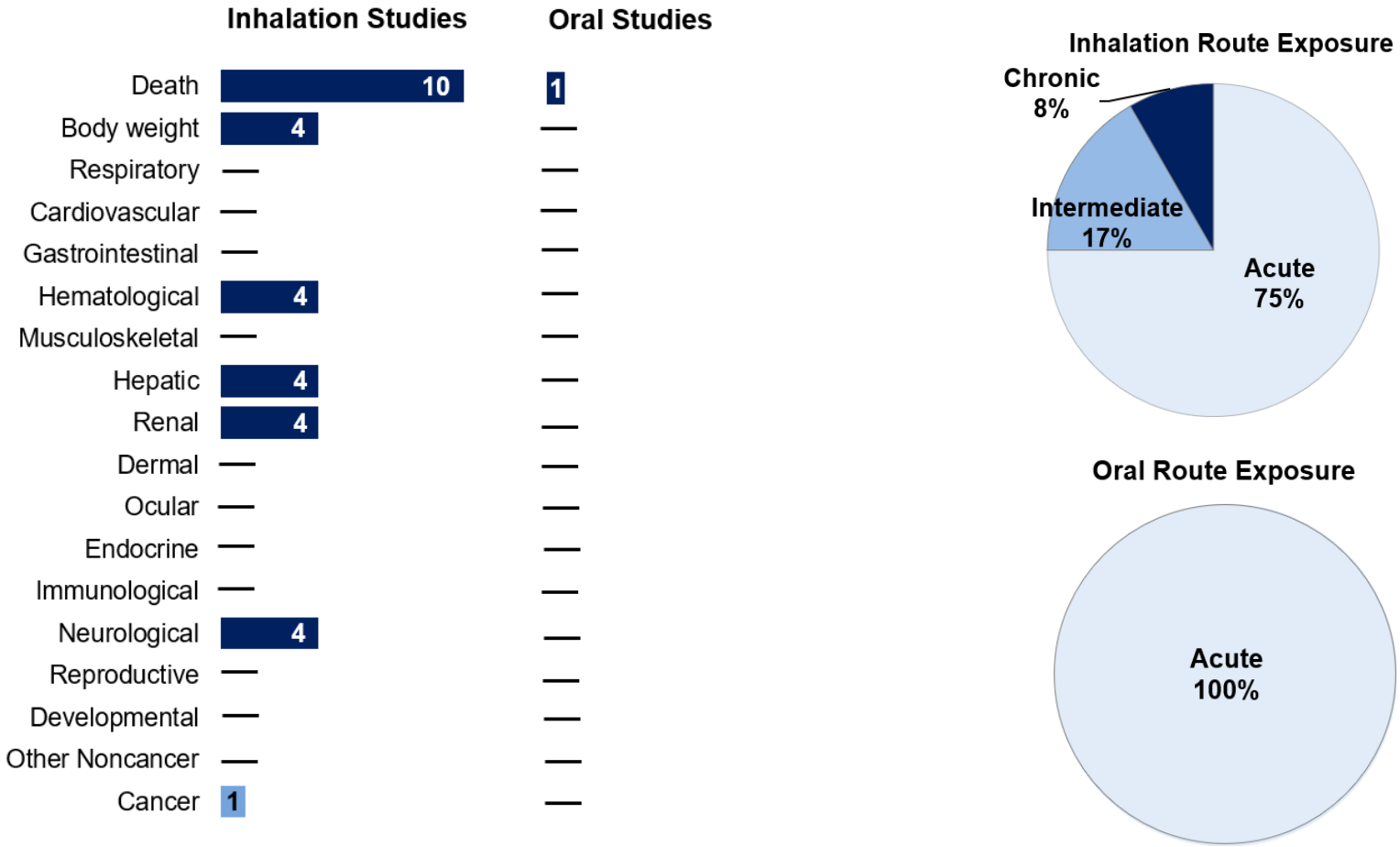
Studies examined oral exposure in **animals** (counts represent studies examining endpoint); no data were identified for **humans** (counts represent studies examining endpoint)



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect. Most studies examined multiple endpoints. No dermal studies in humans or animals were located.

Figure 6-3. Summary of Existing Health Effects Studies for Mixtures of trans- and cis-1,2-Dichloroethene by Route and Endpoint*

Lethality was the most studied endpoint for mixtures of cis- and trans-1,2-dichloroethene
Fewer studies evaluated health effects in humans than animals (counts represent studies examining endpoint)



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect. Most studies examined multiple endpoints. No dermal studies in humans or animals were located.

MRLs.

trans-1,2-Dichloroethene Inhalation MRLs. An acute-duration inhalation MRL was derived for trans-1,2-dichloroethene. Additional studies may provide data to further define the NOAEL-LOAEL boundary. The intermediate-duration inhalation database is inadequate to derive an MRL. Few studies have evaluated potential health effects of intermediate-duration inhalation exposure, and the only reliable study did not identify adverse effects at the highest exposure concentration tested (4,000 ppm). Studies assessing the higher exposure levels may identify effects of intermediate-duration inhalation exposure. No chronic-duration inhalation studies on trans-1,2-dichloroethene were identified; therefore, a chronic-duration inhalation MRL was not derived. Chronic-duration inhalation studies may provide data to develop a chronic-duration MRL for inhaled trans-1,2-dichloroethene.

trans-1,2-Dichloroethene Oral MRLs. An intermediate-duration oral MRL was derived for trans-1,2-dichloroethene; however, additional studies could provide corroborating data for immune effects. For other effects observed in intermediate-duration oral studies for which the biological significance is uncertain (e.g., altered serum glucose and hematological parameters), studies could provide information to determine if effects are toxicologically relevant to human health. An acute-duration oral MRL was not derived, as most studies were designed to assess acute lethality. Studies assessing sublethal effects of acute-duration oral exposure may provide data to develop an acute-duration oral MRL for trans-1,2-dichloroethene. A chronic-duration oral MRL was not derived because no chronic-duration oral exposure studies were identified. Studies assessing effects of chronic-duration oral exposure may provide data for derivation of a chronic-duration oral MRL.

cis-1,2-Dichloroethene Inhalation MRLs. No inhalation MRLs were derived for any exposure duration for cis-1,2-dichloroethene due to inadequate data. Therefore, studies examining comprehensive toxicological endpoints for acute-, intermediate-, and chronic-duration inhalation exposure to cis-1,2-dichloroethene may provide data to develop MRLs.

cis-1,2-Dichloroethene Oral MRLs. No acute-, intermediate-, and chronic-duration oral MRLs were derived for cis-1,2-dichloroethene due to inadequate data. Therefore, studies examining comprehensive toxicological endpoints for all exposure durations may provide data to develop MRLs for cis-1,2-dichloroethene.

Health Effects.

Hematological. A few studies in laboratory animals showed that some hematological parameters may be affected by exposure to trans-1,2-dichloroethene (NTP 2002) or cis-1,2-dichloroethene (McCauley et al. 1990, 1995). However, effects are either very small in magnitude or are not clinically consistent (e.g., decreased hematocrit in the absence of decrease erythrocyte count). Therefore, additional studies to assess effects of exposure to cis- and trans-1,2-dichloroethene may be helpful to determine the relationship between exposure to cis- or trans-1,2-dichloroethene and the hematological system.

Reproductive. No studies were located regarding reproductive toxicity of 1,2-dichloroethene in humans by inhalation, oral, or dermal exposure. In animals, histopathological examination of reproductive tissues did not identify effects of trans-1,2-dichloroethene (DuPont 1998; Hayes et al. 1987; NTP 2002) or cis-1,2-dichloroethene (McCauley et al. 1990, 1995). However, additional studies assessing reproductive function would be useful to determine the potential for cis- and trans-1,2-dichloroethene to produce adverse effects on the reproductive system.

Developmental. One epidemiological study examining developmental effects of *in utero* and possible early life exposure to trans-1,2-dichloroethene did not find associations between exposure and neural tube defect or oral cleft defects (Ruckart et al. 2013). Only one study evaluating developmental effects of trans-1,2-dichhloroethene was identified, and no studies evaluating developmental effects of cis-1,2-dichloroethene were located. The developmental study on trans-1,2-dichloroethene identified resorptions and decreased fetal weight as effects. However, there is uncertainty regarding resorptions because the number of resorptions per litter in the control was below the recent historical range and were within the historical range in the treatment groups. Additional studies may provide data to determine the effects of cis- and trans-1,2-dichloroethene on developmental effects.

Immunotoxicity. One study on trans-1,2-dichloroethene evaluating immunological function was identified, and no studies evaluating immunological effects of cis-1,2-dichloroethene were located. Additional studies could provide supportive data on the immunotoxicity of trans-1,2-dichloroethene and determine if cis-1,2-dichloroethene also affects immune system function.

Epidemiology and Human Dosimetry Studies. A few epidemiological studies have examined general population exposed to trans-1,2-dichloroethene (Ji et al. 2016; Ruckart et al. 2013, 2015).

However, studies of occupational populations were not identified. Additional epidemiological studies on general populations and studies on worker populations could provide important information on the potential effects of 1,2-dichloroethene in humans. Studies could also provide important information on potential dose-response relationships.

Biomarkers of Exposure and Effect. 1,2-Dichlorethene has been detected in blood and expired air. For exposure, it is important to identify methods that can correlate levels of 1,2-dichloroethene in blood or biological tissues and exposure levels. Studies focusing on correlation of blood or urine levels of 1,2-dichloroethene or its metabolites with exposure levels would be useful to facilitate future medical surveillance that can lead to early detection.

No known biomarkers are currently used to characterize effects specifically caused by 1,2-dichloroethene. No unique effects of 1,2-dichloroethene have been identified.

Absorption, Distribution, Metabolism, and Excretion. The absorption, distribution, metabolism, and excretion of 1,2-dichloroethene isomers have not been well-studied. Studies evaluating all toxicokinetic processes could provide data to develop a comprehensive understanding of the toxicokinetics of 1,2-dichloroethene and determine if there are differences between the cis- and trans-isomers.

Comparative Toxicokinetics. Given that few studies have evaluated the toxicokinetics of 1,2-dichloroethene, little information is available to compare potential differences in toxicokinetics between different animal species or between animals and humans. Investigation of 1,2-dichloroethene toxicokinetics in different animal species and comparison of detected metabolites with those detected in occupationally exposed individuals would be useful for determining an appropriate animal model for studying 1,2-dichloroethene.

Children's Susceptibility. Very little information on children's susceptibility to 1,2-dichloroethene is available in humans or animals. General population studies of children exposed *in utero* did not identify associations between exposure and neural tube defect or oral cleft defects or childhood hematopoietic cancers (Ruckart et al. 2013). The only study in animals on susceptibility is a developmental study showing decreased fetal weight. Furthermore, no studies have evaluated how immature drug metabolizing systems could affect children's susceptibility to 1,2-dichloroethene. Additional

developmental studies in animals and studies exposing immature animals to 1,2-dichloroethene may provide additional information to further understand children's susceptibility.

Physical and Chemical Properties. The physical and chemical properties of both cis- and trans-1,2-dichloroethene are well characterized (see Table 4-2) and allow prediction of the transport and transformation of the chemicals in the environment. Therefore, no data needs have been identified at this time.

Production, Import/Export, Use, Release, and Disposal. Current production and import/export volumes and usage data are presently unavailable in the literature. Much of the information regarding 1,2-dichloroethene may be difficult to obtain because many manufacturing companies maintain confidentiality. Production volume submissions for 2020 submitted to the EPA CDR system indicated that 1,2-dichloroethene had a production volume of 1,000,000–<20,000,000 pounds; however, more detailed facts were omitted since they were considered CBI (EPA 2022a). Furthermore, determining the percentage of 1,2-dichloroethene that is used as a captive intermediate (i.e., the 1,2-dichloroethene consumed in closed processes in which the compound is not isolated), as opposed to its use as a solvent, is critical to estimating the amount released to the environment. Differences in toxicity and environmental fate also suggest that isomer-specific information on use and consumption is important. Determination of the levels of 1,2-dichloroethene in consumer products is essential for estimating the exposure of the general population. With up-to-date and accurate production, import/export, and use data, the extent of release into the environment and the potential for human exposure could be more realistically determined. Disposal methods have been described and appear to be satisfactory.

Environmental Fate. 1,2-Dichloroethene released to the environment partitions mainly to the atmosphere (Eisenreich et al. 1981; Swann et al. 1983; Thomas 1982). Important sources of 1,2-dichloroethene include industrial releases and degradation products from other solvents such as trichloroethene, tetrachloroethene, and vinyl chloride (Parsons et al. 1984; Shen 1982b; Smith and Dragun 1984; Vogel et al. 1987). 1,2-Dichloroethene isomers have predicted atmospheric half-lives of 12 days (cis) and 5 days (trans) (Goodman et al. 1986). Both isomers react with hydroxyl radicals in the atmosphere, forming amyl chloride, but atmospheric ozone, nitrate radicals, and singlet oxygen have little environmental effect (Atkinson and Carter 1984). In surface waters, the isomers of 1,2-dichloroethene are rapidly volatilized; half-lives of 5–6.2 hours are estimated for water 1 m deep (Dilling 1977). The compound is not significantly bound to soils or sediments (Barber et al. 1988). Soil-groundwater degradation processes are anaerobic and may involve multiple pathways. Additional information about

the long-term atmospheric fate would be useful, because of the importance of this pathway and the uncertainty of atmospheric degradation processes.

Bioavailability from Environmental Media. No specific information is available regarding human inhalation, oral, or dermal absorption of 1,2-dichloroethene from air, water, food, or soil. Exposure via contaminated drinking water is particularly relevant to humans. Since 1,2-dichloroethene is a neutral lipophilic chemical with a low molecular weight, it probably is readily absorbed through the lungs and gastrointestinal tract. The few available toxicity studies of animals exposed to 1,2-dichloroethene support this hypothesis (Filser and Bolt 1979; Gargas et al. 1988, 1989). No information about human exposure to 1,2-dichloroethene in the environment and the resulting concentrations in human tissue was located. Studies of absorption of 1,2-dichloroethene from air, water, food, and soil in contaminated environments near hazardous waste sites would allow for determination of the rate and extent of absorption from each of these media and for comparison of the potential hazards posed by 1,2-dichloroethene within these media.

Food Chain Bioaccumulation. Few data are available describing the food chain bioaccumulation of 1,2-dichloroethene. Experimental data are unavailable; therefore, it is not known if the bioconcentration potential is consistent with estimated values obtained from regression equations. The estimated BCF of 6 for fathead minnows (Veith and Kosian 1983) suggests that the potential for 1,2-dichloroethene to bioconcentrate is low for aquatic organisms. Therefore, further studies on bioaccumulation are not recommended. However, biomagnification studies would enable scientists to assess the dangers of human exposure to 1,2-dichloroethene from fish and seafood.

Exposure Levels in Environmental Media. Data describing exposure levels in air, surface water, drinking water, groundwater, and soil are limited. 1,2-Dichloroethene has been detected in urban and rural air, air near hazardous waste sites, and indoor air (Grimsrud and Rasmussen 1975; Lipsky and Jacot 1985; Shah and Singh 1988; Vogt and Walsh 1985). 1,2-Dichloroethene is a contaminant monitored for and has current data in the AQS (EPA 2022b). It was one of the original contaminants tested in U.S. drinking water supplies during the first two rounds of the UCMR (EPA 2001). Limited monitoring data of 1,2-dichloroethene in foods are available (FDA 2022b); however, additional monitoring data are needed to better understand potential exposures through ingestion of food sources. Additional indoor air monitoring and vapor intrusion studies have been identified as a data need.

Exposure Levels in Humans. 1,2-Dichloroethene is not a naturally occurring substance. Levels of 1,2-dichloroethene in human blood was below the detection limits for all age and demographic groups in the 2011–2012 NHANES monitoring program (CDC 2021). Information on biological media monitoring of the general population, particularly populations near waste sites, is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Children are expected to be exposed to 1,2-dichloroethene by the same pathways that affect adults. Since 1,2-dichloroethene is denser than air, it is possible that concentrations may be higher at lower levels where crawling or playing children may come in contact with it indoors. However, exposure studies on children are identified as a data need since there are no current studies available.

6.3 Ongoing Studies

No ongoing studies were identified in the National Institute of Health (NIH) RePORTER (2022) database.

CHAPTER 7. REGULATIONS AND GUIDELINES

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

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

Agency	Description	Information	Reference
	Air		
EPA	RfC	Information reviewed but value not estimated	IRIS 2010a, 2010b
WHO	Air quality guidelines	No data	WHO 2010
	Water & Food		
EPA	Drinking water standards and health advisories		EPA 2018a
	1-Day health advisory (10-kg child)		
	cis-1,2-Dichloroethene	4 mg/L	
	trans-1,2-Dichloroethene	20 mg/L	
	10-Day health advisory (10-kg child)		
	cis-1,2-Dichloroethene	3 mg/L	
	trans-1,2-Dichloroethene	2 mg/L	
	DWEL		
	cis-1,2-Dichloroethene	0.07 mg/L	
	trans-1,2-Dichloroethene	0.7 mg/L	
	Lifetime health advisory		
	cis-1,2-Dichloroethene	0.01 mg/L	
	trans-1,2-Dichloroethene	0.1 mg/L	
	10^{-4} Cancer risk	No data	
	National primary drinking water regulations		EPA 2009b
	cis-1,2-Dichloroethene		
	MCL	0.07 mg/L	
	Public health goal	0.07 mg/L	
	trans-1,2-Dichloroethene		
	MCL	0.1 mg/L	
	Public health goal	0.1 mg/L	

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

Agency	Description	Information	Reference
	RfD		
	cis-1,2-Dichloroethene	0.002 mg/kg/day	IRIS 2010a
	trans-1,2-Dichloroethene	0.02 mg/kg/day	IRIS 2010b
	Provisional Peer Reviewed Toxicity Values		EPA 2011c
	cis-1,2-Dichloroethene		
	Provisional subchronic RfD	$2x10^{-2}$ mg/kg/day	
WHO	Drinking water quality guidelines		WHO 2017
	1,2-Dichloroethene		
	guideline value	0.05 mg/L (50 µg/L)	
	TDI	17 µg/kg body weight	
FDA	Substances added to food[a]	Not listed	FDA 2022b
	Indirect food additives regulations 1,2-Dichloroethene (mixed isomers)	Permitted as a component of adhesives	FDA 1996
	Allowable level in bottled water		FDA 2017
	cis-1,2-Dichloroethene	0.07 mg/L	
	trans-1,2-Dichloroethene	0.1 mg/L	
	Cancer		
HHS	Carcinogenicity classification	No data	NTP 2021
EPA	Carcinogenicity classification	Inadequate information to assess carcinogenic potential	IRIS 2010a, 2010b
IARC	Carcinogenicity classification	No data	IARC 2022
	Occupational		
OSHA	PEL (8-hour TWA) for general industry, shipyards and construction		OSHA 2020a, 2020b, 2020c
	1,2-Dichloroethene	200 ppm (790 mg/m^3)	
NIOSH	REL (up to 10-hour TWA)		NIOSH 2019
	1,2-Dichloroethene	200 ppm (790 mg/m^3)	
	IDLH		NIOSH 1994
	1,2-Dichloroethene	1,000 ppm	
	Emergency Criteria		
EPA	AEGLs-air		EPA 2018b
	cis-1,2-Dichloroethene		
	AEGL 1[b]		
	10-minute	140 ppm	
	30-minute	140 ppm	
	60-minute	140 ppm	
	4-hour	140 ppm	
	8-hour	140 ppm	
	AEGL 2[b]		
	10-minute	500 ppm	

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

Agency	Description	Information	Reference
	30-minute	500 ppm	
	60-minute	500 ppm	
	4-hour	340 ppm	
	8-hour	230 ppm	
	AEGL 3[b]		
	10-minute	850 ppm	
	30-minute	850 ppm	
	60-minute	850 ppm	
	4-hour	620 ppm	
	8-hour	310 ppm	
	trans-1,2-Dichloroethene		
	AEGL 1[b]		
	10-minute	280 ppm	
	30-minute	280 ppm	
	60-minute	280 ppm	
	4-hour	280 ppm	
	8-hour	280 ppm	
	AEGL 2[b]		
	10-minute	1,000 ppm	
	30-minute	1,000 ppm	
	60-minute	1,000 ppm	
	4-hour	690 ppm	
	8-hour	450 ppm	
	AEGL 3[b]		
	10-minute	1,700 ppm	
	30-minute	1,700 ppm	
	60-minute	1,700 ppm	
	4-hour	1,200 ppm	
	8-hour	620 ppm	
DOE	PACs-air		DOE 2018a
	1,2-Dichloroethene		
	PAC-1[c]	140 ppm	
	PAC-2[c]	500 ppm	
	PAC-3[c]	850 ppm	
	cis-1,2-Dichloroethene		
	PAC-1[c]	140 ppm	
	PAC-2[c]	500 ppm	
	PAC-3[c]	850 ppm	

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

Agency	Description	Information	Reference
	trans-1,2-Dichloroethene		
	PAC-1[c]	280 ppm	
	PAC-2[c]	1,000 ppm	
	PAC-3[c]	1,700 ppm	

[a]The Substances Added to Food inventory replaces EAFUS and contains the following types of ingredients: food and color additives listed in FDA regulations, flavoring substances evaluated by FEMA or JECFA, GRAS substances listed in FDA regulations, substances approved for specific uses in food prior to September 6, 1958, substances that are listed in FDA regulations as prohibited from use in food, delisted color additives, and some substances "no longer FEMA GRAS".
[b]Definitions of AEGL terminology are available from U.S. Environmental Protection Agency (EPA 2018c).
[c]Definitions of PAC terminology are available from U.S. Department of Energy (DOE 2018b).

AEGL = acute exposure guideline level; DOE = Department of Energy; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; FEMA = Flavor and Extract Manufacturers Association of the United States; 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; JECFA = Joint FAO/WHO Expert Committee on Food Additives; 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; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TDI = tolerable daily intake; TWA = time-weighted average; WHO = World Health Organization

CHAPTER 8. REFERENCES

Aldis H, Osbomy J, Wolf F. 1983. Investigation of soil and water contamination at Western Processing, King County, Washington. In: U.S. Environmental Protection Agency, ed. National conference on management of uncontrolled hazard waste sites: October 31-November 2, 1983. Washington, DC: Hazardous Materials Control Research Institute, 43-53.

Andersen ME, Gargas M, Jones R, et al. 1980. Determination of the kinetic constants for metabolism of inhaled toxicants in vivo using gas uptake measurements. Toxicol Appl Pharmacol 54:100-116. http://doi.org/10.1016/0041-008X(80)90011-3.

Ashley DL, Bonin MA, Cardinali FL, et al. 1994. Blood concentrations of volatile organic compounds in a nonoccupationally exposed US population and in groups with suspected exposure. Clin Chem 40(7 Pt 2):1401-1404. http://doi.org/10.1093/clinchem/40.7.1401.

Atkinson R, Carter WPL. 1984. Kinetics and mechanisms of gas-phase reactions of ozone with organic compounds under atmospheric conditions. Chem Rev 84:437-470. http://doi.org/10.1021/cr00063a002.

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

ATSDR. 2010. Analyses and historical reconstruction of groundwater flow, contaminant fate and transport, and distribution of drinking water within the service areas of the Hadnot Point and Holcomb Boulevard water treatment plants and vicinities, U.S. Marine Corps Base Camp Lejeune, North Carolina. Chapter C: Occurrence of selected contaminants in groundwater at installation restoration program sites. Atlanta, GA: Agency for Toxic Substances and Disease Registry. https://www.atsdr.cdc.gov/sites/lejeune/docs/chapter_c_hadnotpoint.pdf. June 6, 2022.

ATSDR. 2012. Health consultation: MLC former Delphi Division property off-site vapor intrusion investigation Livonia (Wayne County), Michigan. Agency for Toxic Substances and Disease Registry. EPA # MID005356621.

ATSDR. 2022a. 1,2-Dichloroethene. Full SPL data. Substance priority list (SPL) resource page. Agency for Toxic Substances and Disease Registry. https://www.atsdr.cdc.gov/SPL/resources/index.html. June 24, 2022.

ATSDR. 2022b. Sanders2015 HLCs used in SHOWER Model v3 and PHAST. Atlanta, GA: Agency for Toxic Substances and Disease Registry.

Ausbel R, Wijnen MHJ. 1975. Primary steps in the photolysis of cis-1,2-dichloroethylene. Int J Chem Kinet 75:739-751. http://doi.org/10.1002/kin.550070510.

Aylward LL, Kirman CR, Blount BC, et al. 2010. Chemical-specific screening criteria for interpretation of biomonitoring data for volatile organic compounds (VOCs) - Application of steady-state PBPK model solutions. Regul Toxicol Pharmacol 58(1):33-44. http://doi.org/10.1016/j.yrtph.2010.05.011.

Bagley DM, Gossett JM. 1990. Tetrachloroethylene transformation to trichloroethylene and cis-1,2-dichloroethylene by sulfate-reducing enrichment cultures. Appl Env Micro 56(8):2511-2516.

Barber LB, Thurman EM, Schroeder MP, et al. 1988. Long-term fate of organic micropollutants in sewage-contaminated groundwater. Environ Sci Technol 22(2):205-211. http://doi.org/10.1021/es00167a012.

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(4):139-147. http://doi.org/10.1002/bms.1200070402.

Barnes DG, Dourson M. 1988. Reference dose (RfD): Description and use in health risk assessments. Regul Toxicol Pharmacol 8:471-486. http://doi.org/10.1016/0273-2300(88)90047-5.

Barnes DW, Sanders VM, White KL, et al. 1985. Toxicology of trans-1,2-dichloroethylene in the mouse. Drug Chem Toxicol 8(5):373-392. http://doi.org/10.3109/01480548509041065.

Barrio-Lage G, Parsons FZ, Nassar RS, et al. 1986. Sequential dehalogenation of chlorinated ethenes. Environ Sci Technol 20(1):96-99. http://doi.org/10.1021/es00143a013.

Baum G, Oppenlander T. 1995. Vacuum-UV-oxidation of chloroorganic compounds in an excimer flow through photoreactor. Chemosphere 30(9):1781-1790. http://doi.org/10.1016/0045-6535(95)00062-D.

Bennett H. 1981. 1,2-Dichloroethene. In: Encyclopedia of chemical trade names and synonyms. Vol. I. New York, NY: Chemical Publishing Co., 37.

Bennett GF. 1989. Impact of toxic chemicals on local wastewater treatment plant and the environment. Environ Geol Water Sci 13(3):201-212. http://doi.org/10.1007/BF01665370.

Bhopale KK, Falzon M, Ansari GA, et al. 2014. Alcohol oxidizing enzymes and ethanol-induced cytotoxicity in rat pancreatic acinar AR42J cells. In Vitro Cell Dev Biol Anim 50(4):373-380. http://doi.org/10.1007/s11626-013-9700-7.

Blackburn AC, Tzeng HF, Anders MW, et al. 2000. Discovery of a functional polymorphism in human glutathione transferase zeta by expressed sequence tag database analysis. Pharmacogenetics 10(1):49-57. http://doi.org/10.1097/00008571-200002000-00007.

Blackburn AC, Coggan M, Tzeng HF, et al. 2001. GSTZ1d: a new allele of glutathione transferase zeta and maleylacetoacetate isomerase. Pharmacogenetics 11(8):671-678. http://doi.org/10.1097/00008571-200111000-00005.

Boateng K, Evers PC, Testa SM. 1984. Ground water contamination of two production wells: A case history. Ground Water Monit Remediat 4(2):24-31. http://doi.org/10.1111/j.1745-6592.1984.tb00879.x.

Bonse G, Urban T, Reichert D, et al. 1975. Chemical reactivity, metabolic oxirane formation and biological reactivity of chlorinated ethylenes in the isolated perfused rat liver preparation. Biochem Pharmacol 24(19):1829-1834. http://doi.org/10.1016/0006-2952(75)90468-2.

Brenner D. 2010. Results of a long-term study of vapor intrusion at four large buildings at the NASA Ames Research Center. J Air Waste Manag Assoc 60(6):747-758. http://doi.org/10.3155/1047-3289.60.6.747.

Brock WJ. 1990. Acute toxicity studies with trans-1,2-dichloroethylene (DCE). J Am Coll Toxicol 1:10-11.

Brodzinsky R, Singh HB. 1982. 1,2-Dichloroethene. Volatile organic chemical in the atmosphere: An assessment of available data. Menlo Park, CA: SRI International. Contract No. 68-02-3452.

Broholm K, Ludvigsen L, Jensen TF, et al. 2005. Aerobic biodegradation of vinyl chloride and cis-1,2-dichloroethylene in aquifer sediments. Chemosphere 60(11):1555-1564. http://doi.org/10.1016/j.chemosphere.2005.02.056.

Bronzetti G, Bauer C, Corsi C, et al. 1984. Comparative genetic activity of cis- and trans-1,2-dichloroethylene in yeast. Teratog Carcinog Mutagen 4(4):365-375. http://doi.org/10.1002/tcm.1770040406.

Brown KW, Donnelly KC. 1988. An estimation of the risk associated with the organic constituents of hazardous and municipal waste landfill leachates. Haz Waste Haz Mater 55:1-30. http://doi.org/10.1089/hwm.1988.5.1.

Bruce BW, McMahon PB. 1996. Shallow ground-water quality beneath a major urban center: Denver, Colorado, USA. J Hydrol 186(1-4):129-151. http://doi.org/10.1016/s0022-1694(96)03031-4.

Burback BL, Perry JJ. 1993. Biodegradation and biotransformation of groundwater pollutant mixtures by Mycobacterium vaccae. Appl Environ Microbiol 59(4):1025-1029. http://doi.org/10.1128/aem.59.4.1025-1029.1993.

Burk T, Zarus G. 2013. Community exposures to chemicals through vapor intrusion: a review of past agency for toxic substances and Disease Registry public health evaluations. J Environ Health 75(9):36-41.

Bysshe SE. 1982. Bioconcentration factor in aquatic organisms. In: Lyman WJ, Reehl WF, Rosenblatt DH, eds. Handbook of chemical property estimation methods. New York, NY: McGraw Hill Book Co., 5.1-5.30.

Cantelli-Forti G, Bronzetti G. 1988. Mutagenesis and carcinogenesis of halogenated ethylenes. Ann N Y Acad Sci 534:679-693. http://doi.org/10.1111/j.1749-6632.1988.tb30158.x.

CDC. 2021. Fourth national report on human exposure to environmental chemicals: Updated tables, March 2021. Volume two: NHANES 2011-2016. Atlanta, GA: Centers for Disease Control and Prevention. https://www.cdc.gov/exposurereport/index.html. June 23, 2022.

Cerna M, Kypenova H. 1977. Mutagenic activity of chloroethylene analyzed by screening system tests. Mutat Res 46:214-215.

Clark RM, Fronk CA, Lykins BW. 1988. Removing organic contaminants from groundwater. Environ Sci Technol 22(10):1126-1130. http://doi.org/10.1021/es00175a001.

Clewell HJ, Andersen ME. 1985. Risk assessment extrapolations and physiological modeling. Toxicol Ind Health 1(4):111-131. http://doi.org/10.1177/074823378500100408.

Clewell HJ, Andersen ME. 1994. Physiologically-based pharmacokinetic modeling and bioactivation of xenobiotics. Toxicol Ind Health 10(1-2):1-24. http://doi.org/10.1177/074823379401000101.

Cline PV, Viste DR. 1985. Migration and degradation patterns of volatile organic compounds. Waste Manage Res 3:351-360. http://doi.org/10.1016/0734-242X(85)90128-4.

Cole RH, Frederick RE, Healy RP. 1984. Preliminary findings of the priority pollutant monitoring project of the nationwide urban runoff program. J Water Pollut Control Fed 56:898-908.

Costa AK, Ivanetich KM. 1982. The 1,2-dichloroethylenes: Their metabolism by hepatic cytochrome P-450 in vitro. Biochem Pharmacol 31:2093-2102. http://doi.org/10.1016/0006-2952(82)90426-9.

Costa AK, Ivanetich KM. 1984. Chlorinated ethylenes: Their metabolism and effect on DNA repair in rat hepatocytes. Carcinogenesis 5:1629-1636. http://doi.org/10.1093/carcin/5.12.1629.

Crebelli R, Andreoli C, Carere A, et al. 1995. Toxicology of halogenated aliphatic hydrocarbons: Structural and molecular determinants for the disturbance of chromosome segregation and the induction of lipid peroxidation. Chem Biol Interact 98(2):113-129. http://doi.org/10.1016/0009-2797(95)03639-3.

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://doi.org/10.1093/mutage/14.2.207.

Csandy GA, Laib RJ, Filser JG. 1995. Metabolic transformation of halogenated and other alkenes--a theoretical approach. Estimation of metabolic reactivities for in vivo conditions. Toxicol Lett 75(1-3):217-223. http://doi.org/10.1016/0378-4274(94)03174-6.

Dahlberg JA. 1969. The non-sensitized photo-oxidation of trichlorethylene in air. Acta Chem Scand 23:3081-3090.

De Ceaurriz J, Desiles JP, Bonnet P, et al. 1983. Concentration-dependent behavioral changes in mice following short-term inhalation exposure to various industrial solvents. Toxicol Appl Pharmacol 67(3):383-389. http://doi.org/10.1016/0041-008x(83)90322-8.

Dever RJ. 1986. Responding to industrial contamination of groundwater: A case study. J Am Water Works Assoc 78(9):82-86. http://doi.org/10.1002/j.1551-8833.1986.tb05814.x.

Dilling WL. 1977. Interphase transfer processes. II. Evaporation rates of chloromethanes, ethanes, propanes, and propylenes from dilute aqueous solutions. Comparisons with theoretical predictions. Environ Sci Technol 11:405-409. http://doi.org/10.1021/es60127a009.

DOE. 2018a. 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. U.S. Department of Energy. https://edms3.energy.gov/pac/docs/Revision_29A_Table3.pdf. April 12, 2020.

DOE. 2018b. Protective action criteria (PAC) with AEGLs, ERPGs, & TEELs: Rev. 29A, June 2018. U.S. Department of Energy. https://edms3.energy.gov/pac/. April 12, 2020.

DOI. 1983. Organics transported through selected geological media: Assessment of organics transported away from industrial waste disposal sites. Springfield, VA: U.S. Department of the Interior. PB83224246.

Dow Chemical Company. 1960. Results of range finding toxicological tests on 1,2-dichloroethylene, mixed isomers, with cover letter dated 05/10/94 (sanitized). Dow Chemical Company. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0557246. 86940000B36S.

https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0557246.xhtml. October 18, 2022.

Dow Chemical Company. 1994. The toxicity of 1,2-dichloroethylene as determined by repeated exposures on laboratory animals, with cover letter dated 05/10/94 (sanitized). Dow Chemical Company. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0557247. 86940000837S. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0557247.xhtml. October 18, 2022.

Dreher EL, Torkelson TR, Beutel KK. 2012. Chlorethanes and chloroethylenes. In: Ullmann's encyclopedia of industrial chemistry. Vol. 8. Hoboken, NJ: John Wiley & Sons, Inc., 720-788. http://doi.org/10.1002/14356007.o06_o01.

DuPont. 1988a. Acute dermal toxicity study of trans-1,2-dichloroethylene in rabbits with cover letter dated 05/10/94 (sanitized). E.I. Dupont Denemours & Co. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0557172. 86940000762S. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0557172.xhtml. October 18, 2022.

DuPont. 1988b. Skin irritation test in rabbits of trans-1,2-dichloroethylene with cover letter dated 05/10/94 (sanitized). E.I. Dupont Denemours & Co. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0557174. 86940000764S. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0557174.xhtml. October 18, 2022.

DuPont. 1988c. Eye irritation test in rabbits of trans-1,2-dichloroethylene with cover letter dated 05/10/94 (sanitized). E.I. Dupont Denemours & Co. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0557173. 86940000763S.

DuPont. 1998. trans-1,2-Dichloroethylene: 90-day inhalation toxicity study in rats. E.I. du Pont de Nemours and Company, 110-467. Dupont HL-1998-00952. https://www.regulations.gov/comment/EPA-HQ-OPPT-2018-0465-0009. August 23, 2022.

Ehlke TA, Imbrigiotta TE, Wilson BH, et al. 1992. Biotransformation of cis-1,2-dichloroethylene in aquifer material from Picattiny Arsenal, Morris County, New Jersey. In: Mallard GE, Aronson DA, eds. U.S. Geological Survey toxic substances hydrology program--proceedings of the technical meeting, Monterey, California, March 11-15, 1991. WRI 914034. Reston, VA: U.S. Geological Survey, 689-697. http://doi.org/10.3133/wri914034.

Eisenreich SJ, Looney BB, Thornton JD. 1981. Airborne organic contaminants of the Great Lakes ecosystem. Environ Sci Tech 15:30-38. http://doi.org/10.1021/es00083a002.

EPA. 1975. Preliminary assessment of suspected carcinogens in drinking water. Interim report to Congress, June, 1975. Washington, DC: U.S. Environmental Protection Agency. PB250961. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=91012F6P.txt. October 18, 2022.

EPA. 1976. Frequency of organic compounds identified in water. Athens, GA: U.S. Environmental Protection Agency. EPA600476062. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=9100PLS3.txt. October 18, 2022.

EPA. 1978. Quantification of chlorinated hydrocarbons in previously collected air samples. U.S. Environmental Protection Agency. EPA450378112. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=9100IDU1.txt. June 30, 2022.

EPA. 1979. Water related environmental fate of 129 priority pollutants. Vol II. Washington, DC: U.S. Environmental Protection Agency. EPA440479029B. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=2000K6JL.txt. July 1, 2022.

EPA. 1980a. Ambient water quality criteria document for DCE. U.S. Environmental Protection Agency. EPA440580041. https://www.epa.gov/sites/default/files/2019-03/documents/ambient-wqc-dichloroethylenes-1980.pdf. October 18, 2022.

EPA. 1980b. Treatability manual. Vol. 1. Treatability data. Washington, DC: U.S. Environmental Protection Agency. EPA600880042. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=30005R3P.txt. October 18, 2022.

EPA. 1981a. Aquatic fate process data for organic priority pollutants. Washington, DC: U.S. Environmental Protection Agency. EPA440481014. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=9100O12M.txt. October 18, 2022.

EPA. 1981b. Engineering handbook for hazardous waste incineration. Washington, DC: U.S. Environmental Protection Agency. SW889. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=2000KAVZ.txt. June 24, 2022.

EPA. 1981c. Sources of toxic pollutants found in influents to sewage treatment plants. Washington, DC: U.S. Environmental Protection Agency. EPA440481008. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=9101UZJP.txt. August 23, 2022.

EPA. 1983a. Measurements of hazardous organic chemicals in the ambient atmospheric. Menlo Park, CA: U.S. Environmental Protection Agency. EPA600383002. PB83156935. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=91005A4X.txt. October 18, 2022.

EPA. 1983b. Total toxic organics. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 413.02.

EPA. 1984. Data acquisition for environmental transport and fate screening. Menlo Park, CA: U.S. Environmental Protection Agency. EPA600684010. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=9101BZUU.txt. October 18, 2022.

EPA. 1986a. Superfund record of decision (EPA Region 8): Marshall Landfill Site, Boulder County, Colorado, September 1986 report. U.S. Environmental Protection Agency. EPARODR0886008.

EPA. 1986b. Superfund record of decision (EPA Region 5): Forest Waste Disposal Site, Genesee County, Michigan, June 1986. U.S. Environmental Protection Agency. EPARODR058603.

EPA. 1986c. Superfund record of decision (EPA Region 10): Ponders Corner Site, Washington (second remedial action), September 1985. U.S. Environmental Protection Agency. EPARODRlO85006.

EPA. 1986d. Superfund record of decision (EPA Region 4): Hollingsworth Solderless Terminal Company Site, Fort Lauderdale, Florida, April 1986. U.S. Environmental Protection Agency. EPARODR048600.

EPA. 1987a. Superfund record of decision (EPA Region 2): Lang Property, Pemberton Township, New Jersey, September 1986. U.S. Environmental Protection Agency. EPARODR028603.

EPA. 1988a. Superfund record of decision (EPA Region 2): Vega Alta Public Supply-Wells, Puerto Rico (first remedial action), September 1987. U.S. Environmental Protection Agency. EPARODRO287050.

EPA. 1988b. Land disposal restrictions. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 26.

EPA. 1996a. Compendium method TO-17: Determination of volatile organic compounds in ambient air using active sampling onto sorbent tubes. Compendium of methods for the determination of toxic organic compounds in ambient air. Cincinnati, OH: U.S. Environmental Protection Agency. EPA625R96010b. https://www.epa.gov/sites/default/files/2019-11/documents/to-17r.pdf. October 18, 2022.

EPA. 1996b. Method 8260B: Volatile organic compounds by gas chromatography/mass spectrometry (GC/MS). Hazardous waste test methods. U.S. Environmental Protection Agency. SW-846. https://19january2017snapshot.epa.gov/sites/production/files/2015-12/documents/8260b.pdf. August 23, 2022.

EPA. 1996c. Method 8265: Volatile organic compounds in water, soil, soil gas, and air by direct sampling ion trap mass spectrometry (DSITMS). Hazardous waste test methods. U.S. Environmental Protection Agency. SW-846. https://www.epa.gov/sites/default/files/2015-12/documents/8265.pdf. August 23, 2022.

EPA. 2001. Occurrence of unregulated contaminants in public water systems: An initial assessment. U.S. Environmental Protection Agency. EPA815P00001. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=P1009TXB.txt. June 13, 2022.

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. EPA260B05001. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=P100EI4V.txt. June 13, 2022.

EPA. 2009a. General definitions. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 413.02. https://www.govinfo.gov/content/pkg/CFR-2009-title40-vol28/pdf/CFR-2009-title40-vol28-sec413-02.pdf. June 30, 2022.

EPA. 2009b. National primary drinking water regulations. U.S. Environmental Protection Agency. EPA816F090004. https://www.epa.gov/sites/production/files/2016-06/documents/npwdr_complete_table.pdf. September 7, 2017.

EPA. 2010a. Organic chemicals, plastics, and synthetic fibers. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 414. https://www.govinfo.gov/content/pkg/CFR-2010-title40-vol28/pdf/CFR-2010-title40-vol28-part414.pdf. June 30, 2022.

EPA. 2010b. Specialized definitions. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 433.11. https://www.govinfo.gov/content/pkg/CFR-2010-title40-vol29/pdf/CFR-2010-title40-vol29-sec433-11.pdf. June 30, 2022.

EPA. 2011a. Designation, reportable quantities, and notification. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 302. https://www.govinfo.gov/content/pkg/CFR-2011-title40-vol28/pdf/CFR-2011-title40-vol28-part302.pdf. June 30, 2022.

EPA. 2011b. Discarded commercial chemical products, off-specification species, container residues, and spill residues thereof. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 261.33. https://www.govinfo.gov/content/pkg/CFR-2011-title40-vol26/pdf/CFR-2011-title40-vol26-sec261-33.pdf. June 30, 2022.

EPA. 2011c. Provisional peer-reviewed toxicity values for cis-1,2-dichloroethylene. Cincinnati, OH: U.S. Environmental Protection Agency. EPA690R11020F. https://cfpub.epa.gov/ncea/pprtv/documents/Dichloroethylenecis12.pdf. June 15, 2022.

EPA. 2012a. Criteria and standards for the national pollutant discharge elimination system. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 125. https://www.govinfo.gov/content/pkg/CFR-2012-title40-vol23/pdf/CFR-2012-title40-vol23-part125.pdf. June 30, 2022.

EPA. 2012b. Record of decision: White Chemical Corporation, Newark, Essex County, New Jersey (Operable Unit 3 - Groundwater). U.S. Environmental Protection Agency. https://semspub.epa.gov/work/02/123550.pdf. April 13, 2023.

EPA. 2015. OSWER technical guide for assessing and mitigating the vapor intrusion pathway from subsurface vapor sources to indoor air. U.S. Environmental Protection Agency. OSWER Publication 9200.2-154. https://www.epa.gov/sites/default/files/2015-09/documents/oswer-vapor-intrusion-technical-guide-final.pdf. June 16, 2022.

EPA. 2018a. 2018 Edition of the drinking water standards and health advisories. Washington, DC: U.S. Environmental Protection Agency. EPA822S12001. https://www.epa.gov/system/files/documents/2022-01/dwtable2018.pdf. June 15, 2022.

EPA. 2018b. Compiled AEGL values. U.S. Environmental Protection Agency. https://www.epa.gov/sites/production/files/2018-08/documents/compiled_aegls_update_27jul2018.pdf. April 12, 2020.

EPA. 2018c. About acute exposure guideline levels (AEGLs). U.S. Environmental Protection Agency. https://www.epa.gov/aegl/about-acute-exposure-guideline-levels-aegls. July 26, 2018.

EPA. 2020. Final scope of the risk evaluation for trans-1,2-dichloroethylene. U.S. Environmental Protection Agency. EPA740D20007. https://www.epa.gov/sites/default/files/2020-09/documents/casrn_156-60-5_trans-12-dichloroethylene_final_scope.pdf. June 7, 2022.

EPA. 2021a. Definitions and general program requirements. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 122. https://www.govinfo.gov/content/pkg/CFR-2021-title40-vol24/pdf/CFR-2021-title40-vol24-sec122-1.pdf. June 30, 2022.

EPA. 2021b. 2017 National Emissions Inventory: January 2021 updated release, technical support document Research Triangle Park, NC: U.S. Environmental Protection Agency. EPA454R21001. https://www.epa.gov/sites/default/files/2021-02/documents/nei2017_tsd_full_jan2021.pdf. June 29, 2022.

EPA. 2022a. Chemical data reporting under the toxic substances control act. U.S. Environmental Protection Agency. https://www.epa.gov/chemical-data-reporting/access-cdr-data. June 13, 2022.

EPA. 2022b. Air quality system data. U.S. Environmental Protection Agency. https://www.epa.gov/outdoor-air-quality-data. June 13, 2022.

Fain JE, Brakefield LA, Sherman L, et al. 1987. Environmental risk management of land treatment operational units. Haz Waste Haz Mater 4:83-97. http://doi.org/10.1089/hwm.1987.4.83.

FDA. 1996. Indirect food additives: adhesives and components of coatings. Subpart B - Substances for use only as components of adhesives. Food and Drug Administration. Code of Federal Regulations. 21 CFR 175.105. https://www.govinfo.gov/content/pkg/CFR-1996-title21-vol3/pdf/CFR-1996-title21-vol3-sec175-105.pdf. June 15, 2022.

FDA. 2017. Subpart B - Requirements for specific standardized beverages. Bottled water. U.S. Food and Drug Administration. Code of Federal Regulations. 21 CFR 165.110. https://www.gpo.gov/fdsys/pkg/CFR-2017-title21-vol2/pdf/CFR-2017-title21-vol2-sec165-110.pdf. September 7, 2017.

FDA. 2022a. Analytical results of the Total Diet Study. U.S. Food and Drug Administration. https://www.fda.gov/food/total-diet-study/analytical-results-total-diet-study. June 13, 2022.

FDA. 2022b. Substances added to food. U.S. Food and Drug Administration. https://www.cfsanappsexternal.fda.gov/scripts/fdcc/?set=FoodSubstances. January 24, 2022.

Feiler HD, Starch PJ, Southworth R. 1980. Organics in municipal sludges survey of forty cities. In: Proceedings of the national conference on municipal industrial sludge utility disposal. Silvery Spring, MD: U.S. Environmental Protection Agency, 53-57.

Filser JG, Bolt HM. 1979. Pharmacokinetics of halogenated ethylenes in rats. Arch Toxicol 42(2):123-136. http://doi.org/10.1007/BF00316492.

Fogel MM, Taddeo AR, Fogel S. 1986. Biodegradation of chlorinated ethenes by a methane-utilizing mixed culture. Appl Environ Microbial 51:720-724. http://doi.org/10.1128/aem.51.4.720-724.1986.

Frantik E, Hornychova M, Horvath M. 1994. Relative acute neurotoxicity of solvents: isoeffective air concentrations of 48 compounds evaluated in rats and mice. Environ Res 66(2):173-185. http://doi.org/10.1006/enrs.1994.1053.

Freundt KJ, Macholz J. 1978. Inhibition of mixed function oxidases in rat liver by trans- and cis-1,2-dichloroethylene. Toxicology 10:131-139. http://doi.org/10.1016/0300-483X(78)90063-X.

Freundt KJ, Liebaldt GP, Lieberwirth E. 1977. Toxicity studies on trans-1,2-dichloroethylene. Toxicology 7(2):141-153. http://doi.org/10.1016/0300-483X(77)90059-2.

Fusillo TV, Hochreiter JJ, Lord DG. 1985. Distribution of volatile organic compounds in a New Jersey coastal plain aquifer system. Ground Water 23:354-360. http://doi.org/10.1111/j.1745-6584.1985.tb00780.x.

Galli A, Bauer C, Bronzetti G, et al. 1982. [Genetic activity of 1,2-dichloroethylene A. In vitro studies]. Boll Sot Ital Biol Sper 58:860-863. (Italian)

Gargas ML, Seybold PG, Andersen ME. 1988. Modeling the tissue solubilities and metabolic rate constant (Vmax) of halogenated methanes, ethanes, and ethylenes. Toxicol Lett 43(1-3):235-256. http://doi.org/10.1016/0378-4274(88)90031-8.

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(1):87-99. http://doi.org/10.1016/0041-008X(89)90137-3.

Ghassemi M, Qunilivan S, Bachmaier J. 1984. Characteristics of leachates from hazardous waste landfills. J Environ Sci Health A Environ Sci Eng 19(5):579-620. http://doi.org/10.1080/10934528409375180.

Goodenkauf O, Atkinson JC. 1986. Occurrence of volatile organic chemicals in Nebraska groundwater. Ground Water 24(2):231-233. http://doi.org/10.1111/j.1745-6584.1986.tb00999.x.

Goodman MA, Tuazon EC, Atkinson R, et al. 1986. A study of the atmospheric reactions of chloroethanes with OH radicals. In: ACS Division of environmental chemistry 192nd national meeting. American Chemical Society, 169-171.

Gosselin RE, Smith RP, Hodge HC. 1984. 1,2-Dichloroethene. In: Clinical toxicology of commercial products. 5th ed. Baltimore, MD: Williams and Wilkins, 16.

Gossett JM. 1987. Measurement of Henry's Law constant for C1 and C2 chlorinated hydrocarbons. Environ Sci Technol 21:202-206. http://doi.org/10.1021/es00156a012.

Gossett RW, Brown DA, Young DR. 1983. Predicting the bioaccumulation of organic compounds in marine organisms using octanol/water partition coefficients. Mar Pollut Bull 14:387-392. http://doi.org/10.1016/0025-326X(83)90604-5.

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(4-5):249-257. (French)

Granstrom ML, Ahlert RC, Wiesenfeld J. 1984. The relationships between the pollutants in the sediments and in the water of the Delaware and Raritan Canal. Water Sci Technol 16:375-380. http://doi.org/10.2166/wst.1984.0144.

Greim H, Bonse G, Radwan Z, et al. 1975. Mutagenicity in vitro and potential carcinogenicity of chlorinated ethylenes as a function of metabolic oxirane formation. Biochem Pharmacol 224:2013-2017. http://doi.org/10.1016/0006-2952(75)90396-2

Grimsrud EP, Rasmussen RA. 1975. Survey and analysis of halocarbons in the atmosphere by gas chromatography-mass spectrometry. Atmos Environ 9:1014-1017. http://doi.org/10.1016/0004-6981(75)90022-0.

Gürtler RR, Moeller U, Sommer S, et al. 1994. Photooxidation of exhaust pollutants: III. Photooxidation of the chloroethenes: Degradation efficiencies, quantum yields and products. Chemosphere 29(8):1671-1682. http://doi.org/10.1016/0045-6535(94)90314-X.

Hall LW, Hall WS, Bushong SJ, et al. 1987. In-situ striped bass (Morone saxatilis) contaminant and water quality studies in the Potomac River. Aquat Toxicol 10:73-99. http://doi.org/10.1016/0166-445X(87)90016-6.

Hall LC, Mallon B, Hsieh P, et al. 1989. Health risk assessment of trans-1,2-dichloroethylene in California drinking water. Livermore, CA: University of California. DE89007229. UCRL--21062. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/DE89007229.xhtml. June 30, 2022.

Hallen RT, Pyne JW, Molton PM. 1986. Transformation of chlorinated ethenes and ethanes by anaerobic microorganisms. In: ACS division of environmental chemistry 192nd national meeting. American Chemical Society, 344-346.

Hamilton A. 1934. 1,2-Dichloroethene. In: Industrial toxicology. New York, NY: Harper and Brothers Publishers, 217-218.

Hand DW, Crittenden JC, Gehin JL, et al. 1986. Design and evaluation of an air stripping tower for removing VOCs from groundwater. J Am Water Works Assoc 78(9):87-97. http://doi.org/10.1002/j.1551-8833.1986.tb05815.x.

Hanioka N, Jinno H, Nishimura T, et al. 1998. Changes in hepatic cytochrome P450 enzymes by cis- and trans-1,2-dichloroethylenes in rat. Xenobiotica 28(1):41-51. http://doi.org/10.1080/004982598239740.

Hawley GG. 1981. 1,2-Dichloroethene. In: The condensed chemical dictionary. 10th ed. New York, NY: Van Nostrand Reinhold Co., 33.

Hayes JR, Condie LW, Egle JL, et al. 1987. The acute and subchronic toxicity in rats of trans-1,2-dichloroethylene in drinking water. J Am Coll Toxicol 6(4):471-478. http://doi.org/10.3109/10915818709075692.

Hopkins GD, McCarty PL. 1995. Field evaluation of in situ aerobic cometabolism of trichlorethylene and three dichloroethylene isomers using phenol and toluene as the primary substrates. Environ Sci Technol 29(6):1628-1637. http://doi.org/10.1021/es00006a029.

Horvath AL. 1982. 1,2-Dichloroethene. In: Halogenated hydrocarbons solubility - miscibility with water. New York, NY: Marcel Dekker Inc., 496-497.

Hsu CY, Chiang HC, Shie RH, et al. 2018. Ambient VOCs in residential areas near a large-scale petrochemical complex: Spatiotemporal variation, source apportionment and health risk. Environ Pollut 240:95-104. http://doi.org/10.1016/j.envpol.2018.04.076.

Hurtt ME, Valentine R, Alvarez L. 1993. Developmental toxicity of inhaled trans-1,2-dichloroethylene in the rat. Fundam Appl Toxicol 20(2):225-230. http://doi.org/10.1006/faat.1993.1030.

IARC. 2022. Agents classified by the IARC monographs, volumes 1–131. International Agency for Cancer Research. https://monographs.iarc.who.int/list-of-classifications. June 21, 2022.

Illinois ENR. 1984. Investigation of a volatile organic chemical plume in Northern Winnebago County, Illinois. Springfield, IL: Illinois Department of Energy and Natural Resources. PB85114452. ILENRRE8409.

IRIS. 2010a. cis-1,2-Dichloroethylene; CASRN 156-59-2. Integrated Risk Information System. Chemical assessment summary. U.S. Environmental Protection Agency. https://iris.epa.gov/static/pdfs/0418_summary.pdf. October 2, 2017.

IRIS. 2010b. trans-1,2-Dichloroethylene; CASRN 156-60-5. Integrated Risk Information System. Chemical assessment summary. U.S. Environmental Protection Agency. https://iris.epa.gov/static/pdfs/0314_summary.pdf. October 2, 2017.

Janssen DB, Grobben G, Hoekstra R, et al. 1988. Degradation of trans-1,2-dichloroethene in mixed and pure cultures of methanotrophic bacteria. Appl Microbial Biotechnol 29:392-399. http://doi.org/10.1007/BF00265825.

Jeffers PM, Ward LM, Woytowitch LM, et al. 1989. Homogenous hydrolysis rate constants for selected chlorinated methanes, ethanes, ethenes, and propanes. Environ Sci Technol 23:965-969. http://doi.org/10.1021/es00066a006.

Ji G, Xu C, Sun H, et al. 2016. Organochloride pesticides induced hepatic ABCG5/G8 expression and lipogenesis in Chinese patients with gallstone disease. Oncotarget 7(23):33689-33702. http://doi.org/10.18632/oncotarget.9399.

Kallman MJ, Lynch MR, Landauer MR. 1983. Taste aversions to several halogenated hydrocarbons. Neurobehav Toxicol Teratol 5(1):23-27.

Kastner M. 1991. Reductive dechlorination of tri- and tetrachloroethylenes depends on transition from aerobic to anaerobic conditions. Appl Environ Microbiol 57(7):2039-2046. http://doi.org/10.1128/aem.57.7.2039-2046.1991.

Kawamura K, Kaplan IR. 1983. Organic compounds in the rainwater of Los Angeles. Environ Sci Technol 17(8):497-501. http://doi.org/10.1021/es00114a011.

Kernan GJ, Ji BT, Dosemeci M, et al. 1999. Occupational risk factors for pancreatic cancer: a case-control study based on death certificates from 24 U.S. states. Am J Ind Med 36(2):260-270. http://doi.org/10.1002/(sici)1097-0274(199908)36:2<260::aid-ajim5>3.0.co;2-p.

Klier NJ, West RJ, Donberg PA. 1999. Aerobic biodegradation of dichloroethylenes in surface and subsurface soils. Chemosphere 38(5):1175-1188. http://doi.org/10.1016/S0045-6535(98)00485-8.

Koch R, Schlegelmilch R, Wolf HU. 1988. Genetic effects of chlorinated ethylenes in the yeast Saccharomyces cerevisiae. Mutat Res 206(2):209-216. http://doi.org/10.1016/0165-1218(88)90162-0.

Kolpin DW, Squillace PJ, Zogorski JS, et al. 1997. Pesticides and volatile organic compounds in shallow urban groundwater of the United States. In: Chilton D, ed. Groundwater in the urban environment. A.A. Balkema, 469-474.

Krill RM, Sonzogni WC. 1986. Chemical monitoring of Wisconsin's groundwater. J Am Water Works Assoc 78(9):70-75. http://doi.org/10.1002/j.1551-8833.1986.tb05812.x.

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.

Ladics GS. 2007. Use of SRBC antibody responses for immunotoxicity testing. Methods 41(1):9-19. http://doi.org/10.1016/j.ymeth.2006.07.020.

Lam RHF, Brown JP, Fan AM, et al. 1994. Chemicals in California drinking water source contaminants risk assessment, risk management, and regulatory standards. J Hazard Mater 39(2):173-192. http://doi.org/10.1016/0304-3894(94)00053-0.

Lao RC, Thomas RS, Bastien P, et al. 1982. Analysis of organic priority pollutants and non-priority pollutants in environmental samples by GC/MS computer systems. In: Albaiges J, ed. Analytical techniques in environmental chemistry II. New York, NY: Pergamon Press LTD, 107-118.

LaRegina J, Bozzelli JW, Harkov R, et al. 1986. Volatile organic compounds at hazardous waste sites and a sanitary landfill in New Jersey. An up-to-date review of the present situation. Environ Prog 5(1):18-27. http://doi.org/10.1002/ep.670050109.

Lee MD, Thomas JM, Borden RC, et al. 1988. Biorestoration of aquifers contaminated with organic compounds. CRC Crit Rev Environ Control 18(1):29-89. http://doi.org/10.1080/10643388809388342.

Lehmann KB, Schmidt-Kehl L. 1936. [The thirteen most important chlorinated aliphatic hydrocarbons from the standpoint of industrial hygiene]. Arch Hyg 116:132-268. (German)

Leibman KC, Ortiz E. 1977. Metabolism of halogenated ethylenes. Environ Health Perspect 21:91-97. http://doi.org/10.1289/ehp.772191.

Lesage S, Jackson RE, Priddle MW, et al. 1990. Occurrence and fate of organic solvent residues in anoxic groundwater at the Gloucester Landfill, Canada. Environ Sci Technol 24(4):559-566. http://doi.org/10.1021/es00074a016.

Leschber R, Mergler-Voelkl R, Nerger M. 1990. Soil and groundwater contamination by low boiling chlorinated hydrocarbons in Berlin. Formation of metabolites and their analytical determination. Int J Environ Anal Chem 39(2):159-164. http://doi.org/10.1080/03067319008027692.

Lilly PD, Thornton-Manning JR, Gargas ML, et al. 1998. Kinetic characterization of CYP2E1 inhibition in vivo and in vitro by the chloroethylenes. Arch Toxicol 72(10):609-621. http://doi.org/10.1007/s002040050551.

Lipscomb JC, Garrett CM, Snawder JE. 1997. Cytochrome P450-dependent metabolism of trichloroethylene: interindividual differences in humans. Toxicol Appl Pharmacol 142(2):311-318. http://doi.org/10.1006/taap.1996.8040.

Lipsky D, Jacot B. 1985. Hazardous emissions from sanitary landfills. In: Proceedings of 78th annual meeting of the Air Pollution Control Association, June 16-21. Detroit, MI: Air Pollution Control Association, 1-13.

Lue-Hing C, Lordi DT, Kelada NP. 1981. Fate of priority pollutants in large municipal treatment plants. AIChE Symp Ser 77(209):144-150.

Lyman WJ. 1982. Adsorption coefficient for soils and sediments. In: Lyman WJ, Reehl WF, Rosenblatt DH, eds. Handbook of chemical property estimation methods. New York, NY: McGraw Hill Book Co., 4.1-4.33.

McCauley PT, Robinson M, Condie LW, et al. 1990. The effect of subacute and subchronic oral exposure to cis-1,2-dichloroethylene in rats. Cincinnati, OH: U.S. Environmental Protection Agency. Air Force Aerospace Medial Research Laboratory. https://ordspub.epa.gov/ords/eims/eimscomm.getfile?p_download_id=491529. August 23, 2022.

McCauley PT, Robinson M, Daniel FB, et al. 1995. The effects of subacute and subchronic oral exposure to cis-1,2-dichloroethylene in Sprague-Dawley rats. Drug Chem Toxicol 18(2-3):171-184. http://doi.org/10.3109/01480549509014319.

McMillan DA. 1986. Toxicity of the cis and trans isomers of 1,2-dichloroethylene. Partial fulfillment of requirements for the degree of Doctor of Philosophy. Pharmaceutical Sciences. Omaha, NE: University of Nebraska

Michal J. 1976. Toxicity of pyrolysis and combustion products of poly-(vinyl chloride). Fire Mater 1:57-62. http://doi.org/10.1002/fam.810010205.

Milde G, Nerger M, Mergler R. 1988. Biological degradation of volatile chlorinated hydrocarbons in groundwater. Water Sci Technol 20(3):67-73. http://doi.org/10.2166/wst.1988.0083.

Mortelmans K, Haworth S, Lawlor T, et al. 1986. Salmonella mutagenicity tests: II. Results from the testing of 270 chemicals. Environ Mutagen 8(Suppl 7):1-119. http://doi.org/10.1002/em.2860080703.

Mudder TI. 1981. Development of empirical structure-biodegradability relationships and testing protocol for slightly soluble and volatile priority pollutants. Ann Arbor, MI: University Microfilms International.

Mudder TI, Musterman JL. 1982. Development of empirical structure biodegradability relationships and biodegradability testing protocol for volatile and slightly soluble priority pollutants. In: Division of environmental chemistry of the American Chemical Society. Kansas City, MO: American Chemical Society, 52-53.

Munson AE, Sanders VM, Douglas KA, et al. 1982. In vivo assessment of immunotoxicity. Environ Health Perspect 43:41-52. http://doi.org/10.1289/ehp.824341.

Myers VB. 1983. Remedial activities at the Miami Drum Site, Florida. In: Proceedings of the national conference on management of uncontrolled hazardous waste. Washington, DC: U.S. Environmental Protection Agency, 354-335.

Nakahama T, Sarutani S, Inouye Y. 2000. Effects of chlorinated ethylenes on expression of rat CYP forms: Comparative study on correlation between biological activities and chemical structures. J Health Sci 46:251-258. http://doi.org/10.1248/jhs.46.251.

NAS/NRC. 1989. Biologic markers in reproductive toxicology. Washington, DC: National Academy of Sciences/National Research Council. 15-35.

Naylor LM, Loehr RC. 1982. Priority pollutants in municipal sewage sludge. Biocycle 23:18-22.

Nicola RM, Branchflower R, Pierce D. 1987. Chemical contaminants in bottomfish. J Environ Health 49(6):342-347.

NIOSH. 2019. 1,2-Dichloroethylene. NIOSH pocket guide to chemical hazards. National Institute for Occupational Safety and Health. https://www.cdc.gov/niosh/npg/npgd0195.html. June 15, 2022.

NLM. 2022a. PubChem compound summary: cis-1,2-dichloroethylene. National Library of Medicine. https://pubchem.ncbi.nlm.nih.gov/compound/643833. August 24, 2022.

NLM. 2022b. PubChem compound summary: trans-1,2-dichloroethylene. National Library of Medicine. https://pubchem.ncbi.nlm.nih.gov/compound/638186. August 24, 2022.

NOAA. 1980. Quantitation of pollutants in suspended matter and water from Puget Sound. Richland, WA: National Oceanic and Atmospheric Administration. NOAA-80061003. https://repository.library.noaa.gov/view/noaa/11196. October 18, 2022.

NTP. 2002. NTP Technical report on the toxicity studies of trans-1,2-dichloroethylene (CAS No. 156-60-5) administered in microcapsules in feed to F344/N rats and B6C3F$_1$ mice. National Toxicology Program. PB2002108967. NTP Tox 55. https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox055.pdf. October 18, 2022.

NTP. 2013. Draft OHAT approach for systematic review and evidence integration for literature-based health assessments – February 2013. National Toxicology Program, Office of Health Assessment and Translation. https://ntp.niehs.nih.gov/ntp/ohat/evaluationprocess/draftohatapproach_february2013.pdf. (Retrieval in progress)

NTP. 2015. OHAT risk of bias rating tool for human and animal studies. National Toxicology Program, Office of Health Assessment and Translation. https://ntp.niehs.nih.gov/ntp/ohat/pubs/riskofbiastool_508.pdf. March 19, 2019.

NTP. 2021. CASRN index. Report on carcinogens. National Toxicology Program. https://ntp.niehs.nih.gov/pubhealth/roc/index-1.html#P. January 10, 2022.

OECD. 2011. OECD environment, health and safety publications: No. 30 Series on emission scenario documents. Emission scenario document on the chemical industry Paris, France: Organisation for Economic Co-operation and Development. ENV/JM/MONO(2011)49. https://www.oecd.org/env/ehs/risk-assessment/48774702.pdf. June 7, 2022.

OECD. 2015. OECD environment, health and safety publications: No. 34 Series on emission scenario documents. Emission scenario document (ESD) on the use of adhesives. Paris, France: Organisation for Economic Co-operation and Development. ENV/JM/MONO(2015)4. https://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/JM/MONO(2015)4&doclanguage=en. June 7, 2022.

OSHA. 2020a. Occupational safety and health standards. Subpart Z - Toxic and hazardous substances. Air contaminants. Table Z-1: Limits for air contaminants. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1000. https://www.govinfo.gov/content/pkg/CFR-2020-title29-vol6/pdf/CFR-2020-title29-vol6-sec1910-1000.pdf. May 10, 2022.

OSHA. 2020b. Occupational safety and health standards for shipyard employment. Subpart Z - Toxic and hazardous substances. Air contaminants. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1915.1000. https://www.govinfo.gov/content/pkg/CFR-2020-title29-vol7/pdf/CFR-2020-title29-vol7-sec1915-1000.pdf. May 10, 2022.

OSHA. 2020c. Safety and health regulations for construction. Subpart D - Occupational health and environment controls. Gases, vapors, fumes, dusts, and mists. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1926.55. https://www.govinfo.gov/content/pkg/CFR-2020-title29-vol8/pdf/CFR-2020-title29-vol8-sec1926-55.pdf. May 10, 2022.

Otson R. 1987. Purgeable organics in Great Lakes raw and treated water. Int J Environ Anal Chem 31(1):41-53. http://doi.org/10.1080/03067318708077128.

Otson R, Williams DT, Bothwell PD. 1982. Volatile organic compounds in water at thirty Canadian potable water treatment facilities. J Assoc Off Anal Chem 65(6):1370-1374. http://doi.org/10.1093/jaoac/65.6.1370.

Page GW. 1981. Comparison of groundwater and surface water for patterns and levels of contamination by toxic substances. Environ Sci Technol 15(12):1475-1481. http://doi.org/10.1021/es00094a008.

Paolini M, Mesirca R, Pozzetti L, et al. 1992. Selective induction of murine liver cytochrome P450 IIB1 by halogenated hydrocarbons. Toxicol Environ Chem 36(3-4):235-249. http://doi.org/10.1080/02772249209357846.

Parsons F, Wood PR, DeMarco J. 1984. Transformations of tetrachloroethene and trichloroethane in microcosms and groundwater. J Am Water Works Assoc 76(2):56-59. http://doi.org/10.1002/j.1551-8833.1984.tb05282.x.

Peyret T, Krishnan K. 2012. Quantitative property-property relationship for screening-level prediction of intrinsic clearance of volatile organic chemicals in rats and its integration within PBPK models to predict inhalation pharmacokinetics in humans. J Toxicol 2012:286079. http://doi.org/10.1155/2012/286079.

Pleil JD, Lindstrom AB. 1997. Exhaled human breath measurement method for assessing exposure to halogenated volatile organic compounds. Clin Chem 43(5):723-730.

Plumb RH. 1987. A comparison of ground water monitoring data from CERCLA and RCRA sites. Ground Water Monit Remediat 7:94-100. http://doi.org/10.1111/j.1745-6592.1987.tb00968.x.

Pratt GC, Palmer K, Wu CY, et al. 2000. An assessment of air toxics in Minnesota. Environ Health Perspect 108(9):815-825. http://doi.org/10.1289/ehp.00108815.

Rannug A, Alexandrie AK, Persson I, et al. 1995. Genetic polymorphism of cytochromes P450 1A1, 2D6 and 2E1: regulation and toxicological significance. J Occup Environ Med 37(1):25-36. http://doi.org/10.1097/00043764-199501000-00005.

RePORTER. 2022. 1,2-Dichloroethene. National Institutes of Health, Research Portfolio Online Reporting Tools. https://reporter.nih.gov/. June 24, 2022.

Rooney AA, Boyles AL, Wolfe MS, et al. 2014. Systematic review and evidence integration for literature-based environmental health science assessments. Environ Health Perspect 122(7):711-718. http://doi.org/10.1289/ehp.1307972.

Ruckart PZ, Bove FJ, Maslia M. 2013. Evaluation of exposure to contaminated drinking water and specific birth defects and childhood cancers at Marine Corps Base Camp Lejeune, North Carolina: a case-control study. Environ Health 12:104. http://doi.org/10.1186/1476-069x-12-104.

Ruckart PZ, Bove FJ, Shanley E, et al. 2015. Evaluation of contaminated drinking water and male breast cancer at Marine Corps Base Camp Lejeune, North Carolina: a case control study. Environ Health 14:74. http://doi.org/10.1186/s12940-015-0061-4.

Sabel G, Clark T. 1984. Volatile organic compounds as indicators of municipal solid waste leachate contamination. Waste Manag Res 2(2):119-130. http://doi.org/10.1016/0734-242x(84)90135-6.

Sabljic A. 1984. Predictions of the nature and strength of soil sorption of organic pollutants by molecular topology. J Agric Food Chem 32(2):243-246. http://doi.org/10.1021/jf00122a016.

Sanhueza E, Heicklen J. 1975a. Reaction of atomic oxygen (^{3}P) with CCl_2CH_2. J Photochem 4:1-15. http://doi.org/10.1016/0047-2670(75)80010-4.

Sanhueza E, Heicklen J. 1975b. Oxidation of cis- and trans-CHClCHCl. Int J Chem Kinet 7:589-604.

Sato A, Nakajima T. 1979. A structure-activity relationship of some chlorinated hydrocarbons. Arch Environ Health 34(2):69-75. http://doi.org/10.1080/00039896.1979.10667371.

Sawada M, Sofuni T, Ishidate M. 1987. Cytogenetic studies on 1,1-dichloroethylene and its two isomers in mammalian cells in vitro and in vivo. Mutat Res 187(3):157-163. http://doi.org/10.1016/0165-1218(87)90083-8.

Semprini L. 1995. In situ bioremediation of chlorinated solvents. Environ Health Perspect 103(Suppl 5):101-105. http://doi.org/10.1289/ehp.95103s4101.

Shah JJ, Singh HB. 1988. Distribution of volatile organic chemicals in outdoor and indoor air: a national VOCs data base. Environ Sci Technol 22(12):1381-1388. http://doi.org/10.1021/es00177a001.

Shen TT. 1982a. Estimation of organic compound emissions from waste lagoons. J Air Pollut Cont Assoc 32(1):79-82. http://doi.org/10.1080/00022470.1982.10465374.

Shen TT. 1982b. Air quality assessment for land disposal of industrial wastes. Environ Manage 6:297-305. http://doi.org/10.1007/BF01875061.

Shopp GM, Sanders VM, White KL, et al. 1985. Humoral and cell-mediated immune status of mice exposed to trans-1,2-dichloroethylene. Drug Chem Toxicol 8(5):393-407. http://doi.org/10.3109/01480548509041066.

Silka LR, Wallen DA. 1988. Observed rates of biotransformation of chlorinated aliphatics in groundwater. In: Superfund '88, proceedings of the 9th National Conference. Washington, DC: U.S. Environmental Protection Agency, 138-141.

Singh UP, Orban JE. 1987. The Biscayne Aquifer contamination: cleanup and prevention. Water Resour Bull 23(5):879-888. http://doi.org/10.1111/j.1752-1688.1987.tb02966.x.

Smith JA. 1988. Vapor distribution of trichloroethane and related compounds in soil gas above contaminated groundwater at Picatinny Arsenal, New Jersey. Preprints. In: ACS division of environmental chemistry 196th national meeting. American Chemical Society, 376-377.

Smith LR, Dragun J. 1984. Degradation of volatile chlorinated aliphatic priority pollutants in groundwater. Environ Int 10:291-298. http://doi.org/10.1016/0160-4120(84)90134-X.

Snider EH, Manning FS. 1982. A survey of pollutant emission levels in wastewater and residuals from the petroleum refining industry. Environ Int 7:237-258. http://doi.org/10.1016/0160-4120(82)90114-3.

Staples CA, Werner A, Hoogheem T. 1985. Assessment of priority pollutant concentrations in the United States using STORET database. Environ Toxicol Chem 4:31-42. http://doi.org/10.1002/etc.5620040202.

Stenzel M, Gupta US. 1985. Treatment of contaminated groundwaters with granular activated carbon and air stripping. J Air Pollut Control Assoc 35(12):1304-1309. http://doi.org/10.1080/00022470.1985.10466035.

Stevens VL. 1979. 1,2-Dichloroethylene. In: Grayson M, Eckroth D, eds. Kirk-Othmer encyclopedia of chemical technology. Vol. 5. 3rd ed. New York, NY: John Wiley and Sons, 742-745.

Stonebraker RD, Smith AJ. 1980. Containment and treatment of a mixed chemical discharge from the "Valley of the Drum" near Louisville, Kentucky. In: U.S. Environmental Protection Agency, ed. Control of hazardous material spills proceedings of the 1980 national conference on control of hazardous material spills, May 13-15, 1980, Louisville, Kentucky. Louisville, KY: Vanderbilt University, 1-10.

Suffet IH, Brenner L, Cairo PR. 1980. Gas chromatography-mass spectrometry identification of trace organics in Philadelphia, Pennsylvania, USA drinking waters during a two year period. Water Res 14:853-857.

Swann RL, Laskowski DA, McCall PJ, et al. 1983. A rapid method for the estimation of the environmental parameters octanol/water partition coefficient, soil sorption constant, water to air ratio and water solubility. Res Rev 85:17-28. http://doi.org/10.1007/978-1-4612-5462-1_3.

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 1,2-dichloroethylene, 1,1,2-trichloroethane, 1,3-dichloropropane, 1,2,3-trichloropropane and 1,1,3-trichloropropene, 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://doi.org/10.1016/s0165-1218(96)90107-x.

Tandoi V, Distefano TD, Bowser PA, et al. 1994. Reductive dehalogenation of chlorinated ethenes and halogenated ethanes by a high-rate anaerobic enrichment culture. Environ Sci Technol 28(5):973-979. http://doi.org/10.1021/es00054a033.

Thomas RG. 1982. Volatilization from water. In: Lyman WJ, Reehl WF, Rosenblatt DH, eds. Handbook of chemical property estimation methods. New York, NY: McGraw Hill Book Co., 15.11-15.34.

TRI21. 2023. TRI explorer: Providing access to EPA's toxics release inventory data. Washington, DC: Toxics Release Inventory. U.S. Environmental Protection Agency. http://www.epa.gov/triexplorer/. February 16, 2023.

Tuazon EC, Atkinson R, Winer AM, et al. 1984. A study of the atmospheric reaction of 1,3-dichloropropene and other selected organochlorine compounds. Arch Environ Contam Toxicol 13:691-700. http://doi.org/10.1007/BF01055932.

Tuazon EC, Atkinson R, Aschmann SM, et al. 1988. Atmospheric reactions of chloroethenes with the OH radical. Int J Chem Kinet 20:241-265. http://doi.org/10.1002/kin.550200305.

U.S. Army. 1994. Concentration stability of four volatile organic compounds in soil subsamples. U.S. Army Corps of Engineers. ADA280124. Special Report 94-6. https://apps.dtic.mil/sti/pdfs/ADA280124.pdf. August 23, 2022.

U.S. Army. 2018. Long-term monitoring report: CCFTBR0039 (Site 39) Former oil water separator 2-1251: October 2017 Sampling event: Fort Bragg, North Carolina. U.S. Army Corps of Engineers. https://edocs.deq.nc.gov/WasteManagement/DocView.aspx?id=1482295&dbid=0&repo=WasteManagement. June 7, 2022.

USGS. 2006. Volatile organic compounds in the Nation's ground water and drinking-water supply wells. Reston, VA: U.S. Geological Survey. Circular 1292. https://pubs.usgs.gov/circ/circ1292/. May 13, 2022.

Vannelli T, Logan M, Arciero DM, et al. 1990. Degradation of halogenated aliphatic compounds by the ammonia-oxidizing bacterium Nitrosomonas europaea. Appl Environ Microbiol 56(4):1169-1171. http://doi.org/10.1128/aem.56.4.1169-1171.1990.

Veith GD, Kosian P. 1983. Estimating bioconcentration potential from octanol/water partition coefficients. In: MacKay D, ed. Physical behavior of PCBs in the Great Lakes. Ann Arbor, MI: Ann Arbor Science Publishers, 269-282.

Vogel TM, Criddle CS, McCarty PL. 1987. ES Critical Reviews: Transformations of halogenated aliphatic compounds. Environ Sci Technol 21(8):722-736. http://doi.org/10.1021/es00162a001.

Vogt WG, Walsh JJ. 1985. Volatile organic compounds in gases from landfill simulators. In: 78th Annual meeting of the air pollution control association. Detroit, MI: Air Pollution Control Association, 17.

Wang T, Lenahan R, Kanik M, et al. 1985a. The removal of trichloroethylene contaminated groundwater at Vero Beach, Florida. Arch Environ Contam Toxicol 14:719-723. http://doi.org/10.1007/BF01055779.

Wang T, Lenahan R, Kanik M. 1985b. Impact of trichloroethylene contaminated groundwater discharged to the main canal and Indian River Lagoon, Vero Beach, Florida. Bull Environ Contam Toxicol 34:578-586. http://doi.org/10.1007/BF01609779.

Wang H, Xiang Z, Wang L, et al. 2018. Emissions of volatile organic compounds (VOCs) from cooking and their speciation: A case study for Shanghai with implications for China. Sci Total Environ 621:1300-1309. http://doi.org/10.1016/j.scitotenv.2017.10.098.

Weast RC. 1983. 1,2-Dichloroethene. In: CRC handbook of chemistry and physics. 72nd ed. Boca Raton, FL: CRC Press, Inc., C295.

Westrick JJ, Mello JW, Thomas RF. 1984. The groundwater supply survey. J Amer Water Works Assoc 76(5):52-59. http://doi.org/10.1002/j.1551-8833.1984.tb05334.x.

WHO. 2010. Guidelines for indoor air quality: Selected pollutants. 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. World Health Organization. http://apps.who.int/iris/bitstream/10665/254637/1/9789241549950-eng.pdf?ua=1. February 28, 2017.

Wilson BH, Smith GB, Rees JF. 1986. Biotransformations of selected alkylbenzenes and halogenated aliphatic hydrocarbons in methanogenic aquifer material: a microcosm study. Environ Sci Technol 20(10):997-1002. http://doi.org/10.1021/es00152a005.

Wisconsin DNR. 1988. Volatile organic compounds in groundwater and leachate at Wisconsin landfills. Madison, WI: Wisconsin Department of Natural Resources. DNR-004a. WR85R018. https://digital.library.wisc.edu/1711.dl/HLPFVKRI2TMVD87. June 30, 2022.

Wisconsin DNR. 1989. VOC contamination at selected Wisconsin landfills-sampling results and policy implications. Madison, WI: Wisconsin Department of Natural Resource. DNR-004b. https://digital.library.wisc.edu/1711.dl/PD2NNXATSJIRR8N. June 30, 2022.

Wolf F, Gorelik L. 1984. Persistence of synthetic solvent contaminants in a glacial outwash aquifer, Washington State. In: 7th Annual Madison waste conference proceedings. Madison, WI: University of Wisconsin, 116-131.

Wood JA, Porter ML. 1987. Hazardous pollutants in class II landfills. JAPCA 37(5):609-615. http://doi.org/10.1080/08940630.1987.10466250.

Yeh HC, Kastenberg WE. 1991. Health risk assessment of biodegradable volatile organic chemicals: a case study of PCE, TCE, DCE, and VC. J Hazard Mater 27:111-126. http://doi.org/10.1016/0304-3894(91)80024-I.

Zeiger E, Anderson B, Haworth S, et al. 1988. Salmonella mutagenicity tests: IV. Results from the testing of 300 chemicals. Environ Mol Mutagen 11(Suppl 12):1-157. http://doi.org/10.1002/em.2850190603.

Zisook RE, Simmons BD, Vater M, et al. 2020. Emissions associated with operations of four different additive manufacturing or 3D printing technologies. J Occup Environ Hyg 17(10):464-479. http://doi.org/10.1080/15459624.2020.1798012.

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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** trans-1,2-Dichloroethene
CAS Numbers: 156-60-5
Date: August 2023
Profile Status: Final, pre-public comment
Route: Inhalation
Duration: Acute
MRL: 3 ppm (provisional)
Critical Effect: Lacrimation
Reference: Hurtt et al. 1993
Point of Departure: $BMCL_{10}$ of 256.47 ppm
Uncertainty Factor: 100
LSE Graph Key: 1
Species: Rat

MRL Summary: A provisional acute-duration inhalation MRL of 3 ppm was derived for trans-1,2-dichloroethene based on lacrimation in pregnant rats exposed to trans-1,2-dichloroethene on GDs 7–16. The MRL is based on a $BMCL_{10}$ of 256.47 ppm (unadjusted for exposure duration because exposure was concentration dependent) and a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Selection of the Critical Effect: Few animal studies have investigated effects of acute-duration inhalation exposure to trans-1,2-dichloroethene (Freundt et al. 1977; Gradiski et al. 1978; Hurtt et al. 1993). Gradiski et al. (1978) is an acute lethality study designed to estimate the LC_{50} value for a single 6-hour inhalation exposure to trans-1,2-dichloroethene. No information other than the estimated LC_{50} value (21,723 ppm) was reported. Therefore, this study does not provide suitable data for derivation of the acute-duration inhalation MRL. The Freundt et al. (1977) study examined effects of a single 8-hour exposure to 200, 1,000, and 3,000 ppm and 1–2-week exposures (8 hours/day, 5 days/week) to 200 ppm in female rats (n=6). Histological changes to the respiratory tract (capillary hyperemia and alveolar distention) and decreased leukocyte count (24%) were observed at 200 ppm following the single 8-hour exposure. Leukocyte counts were also decreased by 24% at 1,000 ppm (data not reported for 3,000 ppm); therefore, effects did not exhibit dose-dependence. Following exposure to 200 ppm for 1–2 weeks, histological changes were observed to the respiratory tract (capillary hyperemia and alveolar distention), liver (slight fatty accumulation of liver lobules), and immune system (slight fatty accumulation in Kupffer cells). Statistical evaluation of incidence data for hepatic, respiratory, and immune effects (conducted for this report) showed no difference between exposed and control rats after 2 weeks of exposure. In addition, no hepatic effects were observed in a 90-day study in rats exposed up to 4,000 ppm of trans-1,2-dichloroethene. Additional weaknesses of the Freundt et al. (1977) study include: effects were observed in some control animals, and a small number of animals (n=6) were exposed. Given these weaknesses and lack of statistical significance, findings in this study are not considered reliable to serve as the basis of the MRL.

The study by Hurtt et al. (1993) is a well-conducted study designed to evaluate developmental effects following gestational exposure of pregnant rats to 0, 2,000, 6,000, and 12,000 ppm of trans-1,2-dichloroethene on GDs 7–16 (see details below). Dams were evaluated for signs of clinical toxicity and developmental outcomes. NOAEL and LOAEL values for effects observed in this study are summarized Table A-1. The most sensitive effect observed in the Hurtt et al. (1993) study is an ocular irritation effect (lacrimation), with a LOAEL of 2,000 ppm; a NOAEL was not identified. Therefore, lacrimation was selected as the critical effect for acute-duration exposure. Data for lacrimation are summarized in Table A-2. Note that for systemic effects (e.g., effects resulting from absorbed trans-

1,2-dichloroethene), the most sensitive effect is increased resorption, with NOAEL and LOAEL values of 2,000 and 6,000 ppm, respectively. Resorptions per litter were increased ($p \leq 0.05$) in the 6,000 and 12,000 ppm groups relative to control; resorption data also showed a significant trend across exposure concentrations. The study authors did not consider the increase in resorptions to be biologically significant because resorption rate in controls was below historical controls, and the resorption rates in treatment groups were within historical controls for this laboratory for the past 2 years (0.6–1.5). Given the higher LOAEL value for resorptions (compared to lacrimation), and the uncertainty regarding resorptions per litter relative to historical controls, these data would not be considered adequate to serve as the basis for an MRL.

Table A-1. Summary of Effects Observed in Pregnant Rats Exposed to Inhaled trans-1,2-Dichloroethene on GDs 7–16

		NOAEL/LOAEL (ppm)	
System	Effect	NOAEL	LOAEL
Ocular	Lacrimation	ND	2,000
Developmental	Increased resorptions	2,000	6,000
	Decreased fetal body weight (females)	6,000	12,000
Neurological	Lethargy	6,000	12,000
Body weight	Decreased maternal body weight GDs 7–16	6,000	12,000

GD = gestational day; LOAEL = lowest-observed-adverse-effect level; ND = not determined; NOAEL = no-observed-adverse-effect level

Source: Hurtt et al. 1993

Table A-2. Incidence Data for Lacrimation and Resorptions Observed in Female Rats Exposed to trans-1,2-Dichloroethene on GDs 7–16

	Concentration (ppm)			
Effect	0	2,000	6,000	12,000
Incidence of lacrimation[a,b]	0/24	13/24[c]	22/24[c]	24/24[c]
Resorptions per litter[d]	0.3	0.6	0.8[e]	1.1[e]

[a]Number with lacrimation/number of exposed.
[b]Significant trend, p≤0.0001 (Cochran-Armitage test conducted for this report).
[c]Significantly different from control values, p≤0.0001 (Fisher's exact test conducted for this report).
[d]Significant trend, p≤0.05 (Cochran-Armitage test, as reported by Hurtt et al. 1993).
[e]Significantly different from control values, p≤0.05 (Fisher's exact test, as reported by Hurtt et al. 1993).

GD = gestation day

Source: Hurtt et al. 1993

Selection of the Principal Study: As discussed under *Selection of the Critical Effect*, Hurtt et al. (1993), a well-conducted study designed to evaluate developmental effects, provides data that are suitable for derivation of the MRL. Data provided by other studies are not adequate for derivation of the MRL.

Summary of the Principal Study:

Hurtt ME, Valentine R, Alvarez L. 1993. Developmental toxicity of inhaled trans-1,2-dichloroethylene in the rat. Fundam Appl Toxicol 20(2):225-230.

Groups of 24 pregnant rats were exposed to nominal concentrations of 0, 2,000, 6,000, and 12,000 ppm of trans-1,2-dichloroethene for 6 hours per day (whole body inhalation) on GDs 7–16. Mean daily chamber concentrations (data not shown) were within ±5% of nominal concentrations. The following endpoints were assessed in dams: number of pregnant rats; lethality; maternal body weight and feed consumption on GDs 7–16 and 17–22; clinical signs of toxicity on GDs 7–16 and 17–22; liver and uterus weights (GD 22); numbers of resorptions and corpora lutea (GD 22). The following assessments were conducted in fetuses: number of live and dead fetuses; number of males and females per litter; fetal weight; and external, internal, and skeletal malformations and variations.

No maternal deaths occurred. At the end of the exposure period, maternal weight was decreased by 33% in rats exposed to 12,000 ppm, compared to controls. However, on GD 22, body weight in the 12,000 ppm group was similar to controls. Over the exposure period, maternal feed consumption was decreased by 12 and 16% in the 6,000 and 12,000 ppm groups, respectively. For clinical signs of toxicity, lacrimation was increased at all exposure levels relative to control, respectively (see Table A-3); a significant trend across exposure levels was also observed. Brown, periocular staining, due to excessive lacrimation, was observed in the 6,000 ppm (18/24) and 12,000 ppm (22/24) exposure groups. Lethargy was observed in 10/24 dams exposed to 12,000 ppm. Study authors noted that clinical signs of central nervous system depression were observed in the 6,000 and 12,000 ppm groups, although incidence data were not reported; therefore, NOAEL and LOAEL values could not be determined for central nervous system depression. During the post-exposure period, combined alopecia and periocular staining were increased in the 6,000 and 12,000 ppm groups. Resorptions per litter were increased ($p \leq 0.05$) in the 6,000 and 12,000 ppm groups relative to controls (see Table A-3); as discussed above (Selection of the Critical Effect), there is uncertainty regarding the resorptions per litter relative to historical controls. Mean fetal weight in females was decreased by 5.9%, compared to controls, at 12,000 ppm; no effect on mean fetal weight was observed in males. No fetal external, internal, or skeletal malformations or variations were observed at any exposure level.

Selection of the Point of Departure for the MRL: The $BMCL_{10}$ of 256.47 ppm for lacrimation was selected as the basis of the acute-duration inhalation MRL.

Benchmark dose (BMD) modeling was conducted to identify a point of departure (POD) using the incidence data for lacrimation in pregnant rats exposed to trans-1,2-dichloroethene for 6 hours/day on GDs 7–16 (Hurtt et al. 1993). The data were fit to all available dichotomous models in EPA's Benchmark Dose Software (BMDS; version 3.2) using a benchmark response (BMR) with 10% extra risk. Adequate model fit is judged by four criteria: chi-squared goodness-of-fit ($p>0.1$), visual inspection of the dose-response curve, BMCLs (95% lower confidence limit on the benchmark response concentration [BMC]) that is not 10 times lower than the lowest non-zero dose and scaled residual at the data point (except the control) closest to the predefined BMR. Adequate fit to the data was observed for the Dichotomous Hill, Log-Logistic, and Log-Probit models. Among models providing adequate fit, the lowest $BMCL_{10}$ was selected as the POD when the difference between the $BMCL_{10}$ values estimated from these models was ≥3 fold; otherwise, the $BMCL_{10}$ from the model with the lowest Akaike Information Criterion (AIC) was chosen. In accordance with these selection criteria, the Log-Logistic model, a frequentist, unrestricted model, provided the best fit, with the lowest $BMCL_{10}$ of 256.47 ppm (Table A-3). The Log-Logistic model fit is shown in Figure A-1.

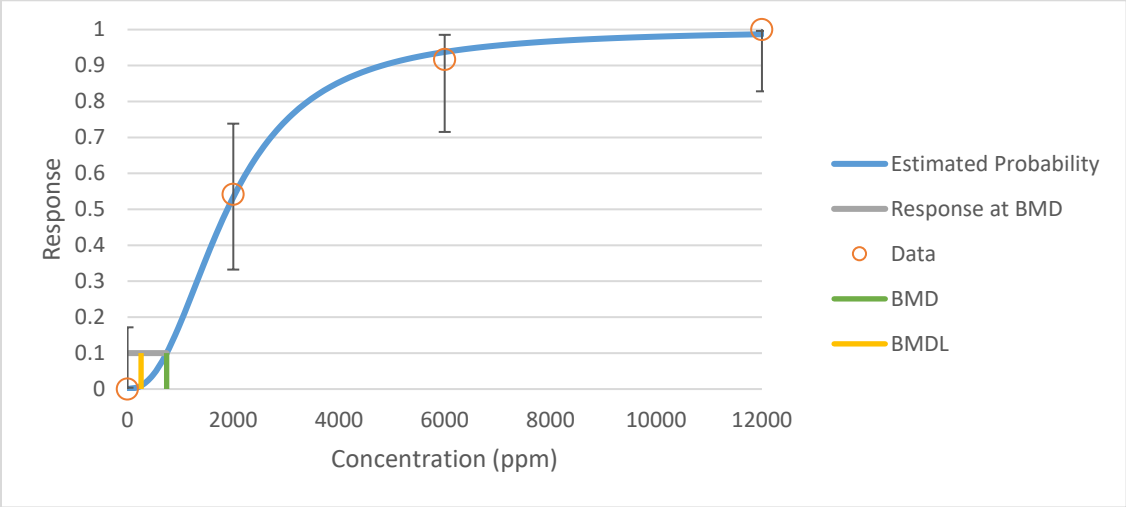
Table A-3. BMD Constant Variance Model Predictions for Lacrimation in Pregnant Crl:CD BR Rats Exposed to trans-1,2-Dichloroethene 6 Hours/Day on GDs 7–16 (Hurtt et al. 1993)

					Scaled residuals[c]	
Model	BMC_{10}[a]	$BMCL_{10}$[a]	p-Value[b]	AIC	Dose below BMC	Dose above BMC
Dichotomous Hill	740.277	256.469	0.479	53.667	-0.001	-0.001
Gamma[d]			0.709	53.103	-0.001	-0.001
Log-Logistic[e,f]	**740.279**	**256.470**	**0.778**	**51.667**	**-0.001**	**-0.001**
Multistage Degree 3[g]			0.835	52.936	-0.001	-0.001
Multistage Degree 2[g]			0.956	51.010	-0.001	-0.001
Multistage Degree 1[g]			0.898	51.252	-0.001	-0.001
Weibull[d]			0.722	53.076	-0.001	-0.001
Logistic			0.047	58.780	-1.583	-1.583
Log-Probit	698.499	230.591	0.571	53.379	-0.001	-0.001
Probit			0.045	58.926	-1.547	-1.547

[a]BMC and BMCLs values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMC.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Selected model. BMCLs for models providing adequate fit differed by <3-fold; therefore, the model with the lowest AIC was selected (Log-Logistic).
[g]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMC = benchmark concentration (maximum likelihood estimate of the concentration associated with the selected benchmark response); $BMCL_{10}$ = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., 10 = dose associated with 10% extra risk; GD = gestation day

Figure A-1. Fit of Log-Logistic Model to Incidence of Lacrimation in Pregnant Crl:CD BR Rats Exposed to trans-1,2-Dichloroethene 6 Hours/Day on Gestation Days 7–16 (Hurt et al. 1993)



Calculations

Intermittent Exposure: Not applicable. The critical effect (lacrimation) is related to the concentration of trans-1,2-dichloroethene in air; therefore, no adjustment was made to a continuous 24-hour exposure.

Human Equivalent Concentration: Not applicable. The critical effect (lacrimation) is related to the concentration of trans-1,2-dichloroethene in air and does not depend upon absorption into the body.

Uncertainty Factor: The $BMCL_{10}$ is divided by a total uncertainty factor of 100:

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

$MRL = BMCL_{10} \div UFs$

$256.47 \text{ ppm} \div (10x10) = 2.6 \text{ ppm} \approx 3 \text{ ppm}$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: An experimental study in two human subjects reported slight burning of the eyes during exposure to trans-1,2-dichloroethene concentrations of approximately 830–2,220 ppm for 30 minutes (Lehmann and Schmidt-Kehl 1936). The dose-response relationship for ocular irritation is uncertain as only two subjects were tested, purity of the test substance was not reported, and precision of methods used to measure trans-1,2-dichloroethene concentrations has not been established. In laboratory animals, instillation of 0.01 mL trans-1,2-dichloroethene to the eyes of rabbits for 20 seconds resulted in ocular irritation, transient severe corneal opacity, moderate iritis, and conjunctivitis (DuPont 1988c).

Agency Contacts (Chemical Manager): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** trans-1,2-Dichloroethene
CAS Numbers: 156-60-5
Date: August 2023
Profile Status: Final, pre-public comment
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration inhalation MRL for trans-1,2-dichloroethene.

Rationale for Not Deriving an MRL: Few studies have assessed the adverse effects of intermediate-duration inhalation exposure to trans-1,2-dichloroethene (DuPont 1998; Freundt et al. 1977). DuPont (1998) did not find any adverse effect in male and female rats (15/group/sex) exposed to concentrations up to 4,000 ppm (6 hours/day, 5 days/week) for 90 days. This study examined comprehensive toxicological endpoints, including histopathologic assessments. Since the DuPont (1998) study did not find adverse effects, it cannot serve as the basis for an intermediate-duration inhalation MRL for trans-1,2-dichloroethene.

The Freundt et al. (1977) study found histological changes to the respiratory tract (capillary hyperemia and alveolar distention), liver (slight fatty accumulation of liver lobules), and immune system (slight fatty accumulation in Kupffer cells) in female rats (n=6) exposed to 200 ppm (8 hours/day, 5 days/week) for 8 or 16 weeks. However, these findings were not corroborated by the DuPont (1998) study at a much higher exposure level (4,000 ppm). In addition, Freundt et al. (1977) has several weaknesses: effects were observed in some control rats; purity of the test substance was not reported so that potential for contaminants in the test substance was not assessed; a small number of animals (n=6) were exposed; and statistical evaluation of the histological data was not presented. Given these weaknesses and lack of corroborating data, findings in this study are not considered reliable.

Agency Contacts (Chemical Manager): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** trans-1,2-Dichloroethene
CAS Numbers: 156-60-5
Date: August 2023
Profile Status: Final, pre-public comment
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration inhalation MRL for trans-1,2-dichloroethene.

Rationale for Not Deriving an MRL: No chronic-duration inhalation studies in humans or animals were identified.

Agency Contacts (Chemical Manager): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** trans-1,2-Dichloroethene
CAS Numbers: 156-60-5
Date: August 2023
Profile Status: Final, pre-public comment
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration oral MRL for trans-1,2-dichloroethene.

Rationale for Not Deriving an MRL: The database of studies evaluating acute-duration oral exposure to trans-1,2-dichloroethene in laboratory animals consists of single dose acute lethality studies (Barnes et al. 1985; Hayes et al. 1987; Munson et al. 1982) and repeated dose studies that did not observe toxicologically significant adverse effects (Barnes et al. 1985; Munson et al. 1982; NTP 2002; Shopp et al. 1985). Acute-duration lethality studies, designed to estimate LD_{50} values, did not report adverse effects at sublethal levels. The only effects observed in repeated dose studies were decreased fibrinogen levels (12%) and prothrombin time (7%) in male mice administered 210 mg/kg/day by gavage for 14 days (Barnes et al. 1985). However, these results are clinically inconsistent. Decreased fibrinogen would be expected to increase prothrombin time (e.g., longer time to formation of fibrinogen clot); however, prothrombin time was decreased. Therefore, the toxicological significance of these findings is uncertain. No adverse hematopoietic or hepatic effects were observed in male and female rats exposed to 5,591 and 4,500 mg/kg/day for 5 days (NTP 2002). Munson et al. (1982) did not observe adverse hematological (including fibrinogen levels and prothrombin time), hepatic, or immunological (humoral and cellular immunity) effects in male mice exposed to 220 mg/kg/day for 20 days. No effects on humoral and cellular immune function were observed in male mice exposed to 210 mg/kg/day for 14 days (Shopp et al. 1985). Therefore, available data are not adequate to derive an acute-duration oral MRL for trans-1,2-dichloroethene.

Agency Contacts (Chemical Manager): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** trans-1,2-Dichloroethene
CAS Numbers: 156-60-5
Date: August 2023
Profile Status: Final, pre-public comment
Route: Oral
Duration: Intermediate
MRL: 0.2 mg/kg/day (provisional)
Critical Effect: Decreased humoral immunity
Reference: Shopp et al. 1985
Point of Departure: $BMDL_{1SD}$ of 16.75 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 13
Species: Mouse

MRL Summary: A provisional intermediate-duration oral MRL of 0.2 mg/kg/day was derived for trans-1,2-dichloroethene based on decreased humoral immunity in male mice exposed to trans-1,2-dichloroethene in drinking water for 90 days. The MRL is based on a $BMDL_{1SD}$ of 16.75 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 Effect: Several studies have evaluated the toxicity of intermediate-duration oral exposure of laboratory animals to trans-1,2-dichloroethene. Reliable NOAEL and LOAEL values are summarized in Table A-4.

Table A-4. Summary of Effects Observed in Laboratory Animals Exposed to Oral trans-1,2-Dichloroethene for Intermediate Durations

Species	Duration (Route)	NOAEL/LOAEL (mg/kg/day) NOAEL	LOAEL	Effect	Reference
Mice (CD-1)	90 days (W)	ND (M) ND (F)	17 (M) 23 (F)	Increased serum glucose	Barnes et al. 1985
Mice (CD-1)	90 days (W)	17 (M) 452 (F)	175 (M) ND (F)	Decreased humoral immunity	Shopp et al. 1985
Rats (F-344)	14 weeks (diet)	190 (M) 780 (F)	380 (M) 1,580 (F)	Decreased erythrocyte counts	NTP 2002
Mice (B6C3F1)	14 weeks (diet)	8,065 (M) 3,760 (F)	ND (M) 7,925 (F)	Decreased terminal body weight	NTP 2002
Rats (Sprague-Dawley)	14 weeks (diet)	3,114 (M) 2,809 (F)	ND (M) ND (F)	No effects observed[a]	Hayes et al. 1987

[a]Evaluations conducted in this study were lethality, body weight, hematological, hepatic, renal, and reproductive endpoints; serum glucose was also assessed.

F = female(s); LOAEL = lowest-observed-adverse-effect level; M = male(s); ND = not determined; NOAEL = no-observed-adverse-effect level; W = drinking water

The lowest LOAEL observed in intermediate-duration oral studies is 17 mg/kg/day for increased serum glucose in male mice exposed for 90 days, although the increase did not exhibit dose-dependence (Barnes et al. 1985). Serum glucose was increased by 27, 20, and 24%, respectively, compared to controls, at doses of 17, 175, and 387 mg/kg/day, respectively. Similar non-dose-dependent increases were observed in females; at doses of 23, 224, and 452 mg/kg/day, serum glucose was increased by 28, 20, and 28%, respectively. In contrast to these findings, no effects on glucose levels were observed in male or female rats at doses up to 3,114 and 2,809 mg/kg/day, respectively, in another study (Hayes et al. 1987). Given that no effects on glucose levels were observed at much higher oral doses in the study by Hayes et al. (1987), the possible relationship between exposure to trans-1,2-dichloroethene and serum glucose levels is uncertain. Therefore, decreased serum glucose was not selected as the critical effect for derivation of the intermediate-duration oral MRL.

The next lowest LOAEL is 175 mg/kg/day for decreased humoral immunity in male mice exposed to trans-1,2-dicloroethene in drinking water for 90 days (Shopp et al. 1985). Suppression in humoral immunity in male mice, as measured by reductions in spleen AFCs directed against sRBCs, was observed at all doses tested; decreases were 6.9, 26, and 26% at doses of 17, 175, and 387 mg/kg/day, respectively. Other tests of immune function (spleen cell response to B cell mitogen lipopolysaccharide and hemagglutination titers) did not show suppression of humoral immunity. However, the sRBC AFC response is considered the "gold standard" for evaluating T-cell-dependent antibody responses and is considered one of the best predictors of immunotoxicity in mice (Ladics 2007).

Other intermediate-duration oral studies identified higher LOAELs than the LOAEL for decreased humoral immunity (175 mg/kg/day). NTP (2002) identified a LOAEL of 380 mg/kg/day in male rats for mild decreases in erythrocyte counts (3.1–7.1%) and a LOAEL of 7,925 mg/kg/day for a 10.7% decreased in terminal body weight in females. Hayes et al. (1987) did not observe any adverse effects at doses up to 3,114 and 2,809 in male and female rats, respectively. Therefore, decreased humoral immunity, with a LOAEL of 175 mg/kg/day for decreased humoral immunity, was selected as the critical effect for derivation of the intermediate-duration oral MRL for trans-1,2-dichhloroethene.

Selection of the Principal Study: As summarized in Table A-4, the lowest LOAELs observed in intermediate-duration oral studies were 17 mg/kg/day for increased serum glucose in male mice exposed for 90 days (Barnes et al. 1985) and 175 mg/kg/day for decreased humoral immunity in male mice (Shopp et al. 1985). As discussed above, the possible relationship between exposure to trans-1,2-dichloroethene and serum glucose levels is uncertain, and effects of serum glucose were not corroborated at much higher doses (Hayes et al. 1987). Other studies either observed effects at doses >175 mg/kg/day or did not identify effects at the highest doses tested (Hayes et al. 1987; NTP 2002). Therefore, the Shopp et al. (1985) study was selected as the principal study for the MRL.

Summary of the Principal Study:

Shopp GM Jr, Sanders VM, White KL, et al. 1985. Humoral and cell-mediated immune status of mice exposed to trans-1,2-dichloroethylene. Drug Chem Toxicol 8:393-407.

Male and female mice were exposed to 0, 0.1, 1.0, or 2.0 mg/mL in drinking water for 90 days; respective daily doses of 0, 17, 175, and 387 mg/kg/day in males and 0, 23, 224, and 452 mg/kg/day in females were calculated by the study authors based on body weight and water intake. Immunological effects of trans-1,2-dichloroethene were evaluated in several assays. The number of animals per group varied for each assay as noted below.

Three assays were used to evaluate the humoral immune status: (1) quantitation of spleen IgM AFCs on days 4 and 5 after *in vivo* exposure to sRBCs (n=12 in control group and n=8 per treatment group);

(2) *ex vivo* hemagglutination titers to sRBC (n=23 in control group and n=6–11 per treatment group); and (3) spleen cell response to the B cell mitogen lipopolysaccharide (LPS) (n=2–9 per group). Cell-mediated immunity was evaluated in three assays: (1) delayed-type hypersensitivity response to sRBC (n=16–19 per group); (2) popliteal lymph node proliferation in response to sRBC (n=11–20 per group); and (3) spleen cell response to the T cell mitogen concanavalin (ConA) (n=2–9 per group). In addition, the following were assessed: number of peritoneal exudate cells (PEC) recruited; number of PEC to adhere to plastic; chemotactic ability of the recruited cells; and phagocytic ability of the adherent cells. The functional ability of the fixed macrophages of the reticuloendothelial system was assessed by measuring the vascular clearance rate and tissue rate of ^{51}Cr-labeled sRBC (thymus, bone marrow).

Results of the humoral immune assay for spleen IgM AFC on days 4 and 5 after *in vivo* exposure to sRBC showed a decreased response in male mice, but not female mice. Expressed in terms of AFC/spleen weight, the day 4 response showed decreased responses at all doses and the day 5 response showed a decreased response at the highest dose. Expressed in terms of AFC/10^6 spleen cells, the day 4 response was decreased in the mid- and high-dose groups and the day 5 response was decreased at the highest dose. Although no statistically significant change in spleen weight was observed, this was confounded by variations in spleen weight. Therefore, results expressed in terms of AFC/10^6 spleen cells are considered more reliable than AFC/spleen weight. In addition, the response to sRBC challenge on day 4 appears to be more sensitive than on day 5. Results of this day 4 assay are summarized in Table A-5.

Table A-5. Antibody-Forming Cell Response to sRBC in Male CD-1 Mice Exposed to trans-1,2-Dichloroethene in Drinking Water for 90 Days[a]

	Dose (mg/kg/day)			
	0	17	175	387
AFC/10^6 spleen cells	2,200±125[b]	2,048±152 (6.9)	1,625±136[c] (26)	1,618±226[b] (26)

[a]Responses were observed on day 4 after *in vivo* exposure to sRBC.
[b]Mean±SE; numbers in parentheses are the percent decreased relative to control; n=12 for control group and n=8 for all other groups.
[c]$p<0.05$.

AFC = antibody-forming cell; SE = standard error; sRBC = sheep red blood cell

Source: Shopp et al. (1985)

Selection of the Point of Departure for the MRL: The $BMDL_{1SD}$ of 16.75 mg/kg/day for decreased humoral response was selected as the basis of the intermediate-duration oral MRL.

BMD modeling was conducted to identify the POD from incidence data for humoral response to sRBC in male mice exposed orally to trans-1,2-dichloroethene for 90 days. The data were fit to all available continuous models in EPA's BMDS (version 3.2) using a BMR of 1 standard deviation. Adequate model fit is judged by four criteria: chi squared goodness-of-fit ($p>0.1$), visual inspection of the dose-response curve, BMDL (95% lower confidence limit on the BMD) that is not 10 times lower than the lowest non-zero dose, and scaled residual at the data point (except the control) closest to the predefined BMR. Among the models providing adequate fit to the data, the lowest BMDL was selected as the POD when the difference between the BMDLs estimated from these models was ≥3 fold; otherwise, the BMDL from the model with the lowest AIC was chosen. The Exponential 4 (CV-normal) model provided the best fit. The model predictions for the humoral response to sRBC are presented in Table A-6 and the fit of the

selected model (Exponential 4) is presented Figure A-2. Note that the $BMDL_{1SD}$ of 16.75 mg/kg/day is essentially identical to the empirical NOAEL of 17 mg/kg/day.

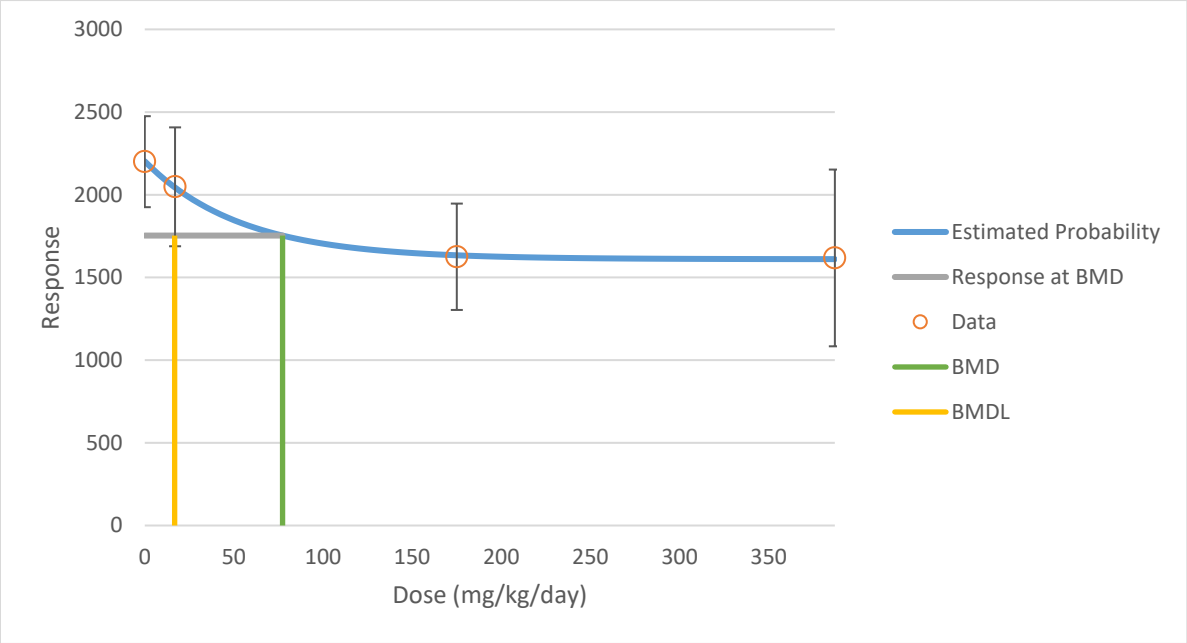
Table A-6. Results from BMD Analysis (Constant Variance) of Humoral Immune Response to Sheep Red Blood Cells in Male CD-1 Mice Exposed to trans-1,2-Dichloroethene in Drinking Water for 90 days (Shopp et al. 1985)

Model	BMD_{1SD}[a] (mg/kg/day)	$BMDL_{1SD}$[a] (mg/kg/day)	Test 4 p-value[b]	AIC	Scaled residuals[c]	
					Dose below BMD	Dose above BMD
Exponential 2[d]	284.039	164.570	0.314	550.161	0.652	0.625
Exponential 3[d]	284.051	164.568	0.314	550.161	0.652	0.625
Exponential 4[d,e]	**77.273**	**16.752**	**0.936**	**549.849**	**0.030**	**-0.016**
Exponential 5[d]			NA	551.843	-0.007	0.005
Hill[d]			NA	551.843	0.000	0.000
Polynomial Degree 3[d]	309.206	195.007	0.260	550.540	0.596	0.721
Polynomial Degree 2[d]	309.207	195.005	0.260	550.540	0.596	0.721
Power[d]	309.205	195.014	0.260	550.540	0.596	0.721
Linear	309.206	195.005	0.260	550.540	0.596	0.721

[a]BMD and BMDLs values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet adequate fit.
[c]Scaled residuals at doses immediately below and above the BMD.
[d]Restricted model.
[e]Recommended model. The difference between the BMDLs estimated from these models was ≥3 fold, therefore the lowest $BMDL_{1SD}$ of models with adequate fit was selected.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{1SD}$ = exposure dose associated with a 1 standard deviation change from the control); NA = not applicable, goodness-of-fit test could not be performed

Figure A-2. Fit of Exponential 4 (Constant Variance) Model to Humoral Immune Response to Sheep Red Blood Cells in Male Mice Exposed to trans-1,2-Dichloroethene in Drinking Water for 90 Days (Shopp et al. 1985)



Calculations

Adjustment for Intermittent Exposure: Not applicable.

Uncertainty Factor: The $BMDL_{1SD}$ is divided by a total uncertainty factor of 100:

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

$MRL = BMDL_{1SD} \div UFs$

$16.75 \text{ mg/kg/day} \div (10x10) = 0.2 \text{ mg/kg/day}$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: The Shopp et al. (1985) study was the only intermediate-duration oral study that evaluated humoral immunity. No supporting studies were identified.

Agency Contacts (Chemical Manager): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** trans-1,2-Dichloroethene
CAS Numbers: 156-60-5
Date: August 2023
Profile Status: Final, pre-public comment
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration oral MRL for trans-1,2-dichloroethene.

Rationale for Not Deriving an MRL: Two epidemiological studies have investigated effects of chronic-duration oral exposure to trans-1,2-dichloroethene (Ji et al. 2016; Ruckart et al. 2013). An increased risk of gallstone disease was positively associated with trans-1,2-dichloroethene levels in adipose tissue in a case-control study of the general population (Ji et al. 2016). Results were stratified by quartiles based on the concentration of trans-1,2-dichloroethene in adipose tissue (ng/g lipid weight): Q1 12.82–721.7; Q2 721.7–1,351; Q3 1,351–2,558; and Q4 2,558–18,135. ORs were increased ($p \leq 0.05$) in Q2 (3.49; 95% CI 1.93, 6.33), Q3 (2.38; 95% CI 1.32, 4.27), and Q4 (2.48; 95% CI 1.38, 4.46), respectively, relative to Q1. In addition, the concentration of trans-1,2-dichloroethene in adipose tissue of patients with gallstone disease (mean: 1,542 ng/g lipid weight) was significantly higher ($p=0.008$) compared to patients without gallstone disease (mean: 1,213 ng/g lipid weight). However, concentrations of trans-1,2-dichloroethene in adipose tissue have not been correlated with blood levels or external exposure concentrations. Ruckart et al. (2013) did not find an association between exposure to trans-1,2-dichloroethene and birth defects (neural tube defect or oral cleft defects) in children born to mothers exposed during pregnancy to trans-1,2-dichloroethene in drinking water. Based on the available epidemiological studies, data are inadequate for derivation of a chronic-duration oral MRL.

No chronic-duration oral studies in animals were identified.

Agency Contacts (Chemical Manager): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** cis-1,2-Dichloroethene
CAS Numbers: 156-60-5
Date: August 2023
Profile Status: Final, pre-public comment
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration inhalation MRL for cis-1,2-dichloroethene.

Rationale for Not Deriving an MRL: No adequate acute-duration inhalation studies were identified for cis-1,2-dichloroethene. Thus, an acute-duration inhalation MRL cannot be derived.

Agency Contacts (Chemical Manager): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** cis-1,2-Dichloroethene
CAS Numbers: 156-60-5
Date: August 2023
Profile Status: Final, pre-public comment
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration inhalation MRL for cis-1,2-dichloroethene.

Rationale for Not Deriving an MRL: No intermediate-duration inhalation studies in humans or animals were identified.

Agency Contacts (Chemical Manager): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** cis-1,2-Dichloroethene
CAS Numbers: 156-60-5
Date: August 2023
Profile Status: Final, pre-public comment
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration inhalation MRL for cis-1,2-dichloroethene

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

Agency Contacts (Chemical Manager): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** cis-1,2-Dichloroethene
CAS Numbers: 156-60-5
Date: August 2023
Profile Status: Final, pre-public comment
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration oral MRL for cis-1,2-dichloroethene.

Rationale for Not Deriving an MRL: One study evaluating acute-duration oral exposure of cis-1,2-dichloroethene was identified (McCauley et al. 1990, 1995). In this study, male and female rats (10/sex/group) were exposed to 0, 97, 290, 970, and 1,900 mg/kg/day cis-1,2-dichloroethene in corn oil by gavage for 14 days. Effects were observed in the hematological, hepatic, and neurological systems.

Hematological effects. Assessment of hematological parameters found that hematocrit was decreased by 11% at doses of 290, 970, and 1,900 mg/kg/day, relative to controls, in female rats; however, no decreases were observed for erythrocyte count or hemoglobin concentration. The toxicological significance of decreased hematocrit in the absence of decreased erythrocyte counts and hemoglobin is uncertain. No hematological effects were observed in males administered up to 1,900 mg/kg/day for 14 days.

Hepatic effects. No histopathological findings were observed in the liver in male or female rats. Increases in relative liver weights were observed in both males and females and ranged from 15% at 97 mg/kg/day to 38% at 1,900 mg/kg/day. In addition, cholesterol was increased by 40% in female, but not in male, rats at the highest dose tested of 1,900 mg/kg/day. However, given the absence of histopathological changes or changes in serum liver enzymes (AP, ALT, AST), the toxicological significance of increased relative liver weights and cholesterol cannot be determined.

Neurological effects. Clinical signs of neurotoxicity (lethargy and ataxia) were observed in the "high dose groups;" however, NOAEL and LOAEL values could not be determined because incidence data were not reported. No histopathological findings were observed in brain tissue.

Results of the 14-day oral study by McCauley et al. (1990, 1995) do not provide suitable data to derive an acute-duration oral MRL for cis-1,2-dichloroethene.

Agency Contacts (Chemical Manager): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** cis-1,2-Dichloroethene
CAS Numbers: 156-60-5
Date: August 2023
Profile Status: Final, pre-public comment
Route: Oral
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration oral MRL for cis-1,2-dichloroethene.

Rationale for Not Deriving an MRL: One study evaluating intermediate-duration oral exposure of cis-1,2-dichloroethene was identified (McCauley et al. 1990, 1995). In this study, male and female rats (10/sex/group) were exposed to 0, 32, 97, 290, and 870 mg/kg/day cis-1,2-dichloroethene in corn oil by gavage for 90 days. Body weight and hematological effects were observed.

Body weight effects. At the highest dose tested, body weight gain in male rats was decreased by 37%, compared to controls. However, terminal body weight in this group was similar to terminal body weight of the control group. Therefore, the decrease in body weight gain does not appear to be toxicologically significant. No treatment-related effects on body weight gain or terminal body weight were observed in female rats.

Hematological effects. Hematocrit and hemoglobin concentration were decreased in male and female rats. In male rats, hematocrit was decreased by 5.8, 8.9, and 8.9% at doses of 290, 970, and 1,900 mg/kg/day, respectively, and hemoglobin concentration was decreased by 6.0% at doses of 970 and 1,900 mg/kg/day. No effects on erythrocyte count were observed. In female rats, hematocrit was decreased by 9.9 and 6.5% at doses of 290 and 870 mg/kg/day, respectively; erythrocyte counts and hemoglobin concentration were decreased by 5.9 and 3.9%, respectively, in the 290 mg/kg/day group, but not in the 870 mg/kg/day group, indicating that these changes were not related to treatment with cis-1,2-dichloroethene. The toxicological significance of decreased hematocrit and hemoglobin concentration in the absence of decreased erythrocyte count is uncertain.

Based results of the McCauley et al. (1990, 1995) study, data are not adequate for derivation of an intermediate-duration oral MRL for cis-1,2-dichloroethene.

Agency Contacts (Chemical Manager): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** cis-1,2-Dichloroethene
CAS Numbers: 156-60-5
Date: August 2023
Profile Status: Final, pre-public comment
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration oral MRL for cis-1,2-dichloroethene

Rationale for Not Deriving an MRL: No chronic-duration oral studies in humans or animals were identified.

Agency Contacts (Chemical Manager): Malcolm Williams

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

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 1,2-dichloroethene.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen were conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for 1,2-dichloroethene. 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 1,2-dichloroethene 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 1,2-dichloroethene 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
Potential for human exposure
Releases to the environment
Air
Water
Soil
Environmental fate
Transport and partitioning
Transformation and degradation
Environmental monitoring
Air
Water
Sediment and soil
Other media
Biomonitoring
General populations
Occupation populations

B.1.1 Literature Search

The current literature search was intended to update the draft toxicological profile for 1,2-dichloroethene; thus, the literature search was restricted to studies published between January 1994 and October 2021. The following main databases were searched in October 2021:

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

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for 1,2-dichloroethene. 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 1,2-dichloroethene 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	
10/2021	((540-59-0[rn] OR 156-59-2[rn] OR 156-60-5[rn] OR "1,2-DCE"[tw] OR "1,2-Dichlor-aethen"[tw] OR "1,2-Dichloroethene"[tw] OR "1,2-Dichloroethylene"[tw] OR "Acetylene dichloride"[tw] OR "Dichloro-1,2-ethylene"[tw] OR "Dioform"[tw] OR "sym-Dichloroethylene"[tw] OR "(Z)-1,2-Dichloroethene"[tw] OR "(Z)-1,2-Dichloroethylene"[tw] OR "Acetalyne dichloride"[tw] OR "cis-Acetylene dichloride "[tw] OR "cis-1,2-Dichloroethene"[tw] OR "cis-1,2-Dichloroethylene"[tw] OR "cis-Dichloroethylene"[tw] OR "HCC 1130c"[tw] OR "R 1130c"[tw] OR "(1Z)-1,2-dichloro-Ethene "[tw] OR "1,2-Dichloroethylene"[tw] OR "(E)-1,2-Dichloroethene"[tw] OR "(E)-1,2-Dichloroethylene"[tw] OR "HCC 1130t"[tw] OR "R 1130t"[tw] OR "trans-1,2-Dichloroethene"[tw] OR "trans-1,2-Dichloroethylene"[tw] OR "trans-Acetylene dichloride"[tw] OR "trans-Dichloroethylene"[tw] OR "(1E)-1,2-dichloro-Ethene"[tw] OR "1,2-Dichloroethylene"[tw] OR "1,2-trans-Dichloroethylene"[tw]) AND (1994/01/01 : 3000[dp] OR 1994/01/01 : 3000[mhda] OR 1994/01/01 : 3000[edat])) OR ((("Dichloroethenes"[tw] OR "Dichloroethene"[tw] OR "Dichloroethylene"[tw] OR "1,2-Dichloroethylene"[tw]) AND (1994/01/01 : 3000[dp] OR 1994/01/01 : 3000[mhda] OR 1994/01/01 : 3000[edat])) NOT medline[sb])
Toxline	
05/2017	("1 2-dce" OR "1 2-dichlor-aethen" OR "1 2-dichloroethene" OR "1 2-dichloroethylene" OR "acetylene dichloride" OR "dichloro-1 2-ethylene" OR "dioform" OR "sym-dichloroethylene" OR " (z) -1 2-dichloroethene" OR " (z) -1 2-dichloroethylene" OR "acetalyne dichloride" OR "cis-acetylene dichloride " OR "cis-1 2-dichloroethene" OR "cis-1 2-dichloroethylene" OR "cis-dichloroethylene" OR "hcc 1130c" OR "r 1130c" OR " (1z) -1 2-dichloro-ethene " OR "1 2-dichloroethylene" OR " (e) -1 2-dichloroethene" OR " (e) -1 2-dichloroethylene" OR "hcc 1130t" OR "r 1130t" OR "trans-1 2-dichloroethene" OR "trans-1 2-dichloroethylene" OR "trans-acetylene dichloride" OR "trans-dichloroethylene" OR " (1e) -1 2-dichloro-ethene" OR "1 2-dichloroethylene" OR "1 2-trans-dichloroethylene" OR "dichloroethenes" OR "dichloroethene" OR "dichloroethylene" OR "1 2-dichloroethylene" OR 540-59-0 [rn] OR 156-59-2 [rn] OR 156-60-5 [rn] OR 25323-30-2 [rn]) AND 1999:2017 [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]
	("1 2-dce" OR "1 2-dichlor-aethen" OR "1 2-dichloroethene" OR "1 2-dichloroethylene" OR "acetylene dichloride" OR "dichloro-1 2-ethylene" OR "dioform" OR "sym-dichloroethylene" OR " (z) -1 2-dichloroethene" OR " (z) -1 2-dichloroethylene" OR "acetalyne dichloride" OR "cis-acetylene dichloride " OR "cis-1 2-dichloroethene" OR "cis-1 2-dichloroethylene"

Table B-2. Database Query Strings

Database search date	Query string
	OR "cis-dichloroethylene" OR "hcc 1130c" OR "r 1130c" OR " (1z) -1 2-dichloro-ethene " OR "1 2-dichloroethylene" OR " (e) -1 2-dichloroethene" OR " (e) -1 2-dichloroethylene" OR "hcc 1130t" OR "r 1130t" OR "trans-1 2-dichloroethene" OR "trans-1 2-dichloroethylene" OR "trans-acetylene dichloride" OR "trans-dichloroethylene" OR " (1e) -1 2-dichloro-ethene" OR "1 2-dichloroethylene" OR "1 2-trans-dichloroethylene" OR "dichloroethenes" OR "dichloroethene" OR "dichloroethylene" OR "1 2-dichloroethylene" OR 540-59-0 [rn] OR 156-59-2 [rn] OR 156-60-5 [rn] OR 25323-30-2 [rn]) AND 1994:1998 [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]
NTRL	
10/2021	"1,2-DCE" OR "1,2-Dichlor-aethen" OR "1,2-Dichloroethene" OR "1,2-Dichloroethylene" OR "Acetylene dichloride" OR "Dichloro-1,2-ethylene" OR "Dioform" OR "sym-Dichloroethylene" OR "(Z)-1,2-Dichloroethene" OR "(Z)-1,2-Dichloroethylene" OR "Acetalyne dichloride" OR "cis-Acetylene dichloride" OR "cis-1,2-Dichloroethene" OR "cis-1,2-Dichloroethylene" OR "cis-Dichloroethylene" OR "HCC 1130c" OR "R 1130c" OR "(1Z)-1,2-dichloro-Ethene " OR "1,2-Dichloroethylene" OR "(E)-1,2-Dichloroethene" OR "(E)-1,2-Dichloroethylene" OR "HCC 1130t" OR "R 1130t" OR "trans-1,2-Dichloroethene" OR "trans-1,2-Dichloroethylene" OR "trans-Acetylene dichloride" OR "trans-Dichloroethylene" OR "(1E)-1,2-dichloro-Ethene" OR "1,2-Dichloroethylene" OR "1,2-trans-Dichloroethylene" OR "Dichloroethenes" OR "Dichloroethene" OR "Dichloroethylene"
Toxcenter	
10/2021	FILE 'TOXCENTER' ENTERED AT 14:43:29 ON 05 OCT 2021 CHARGED TO COST=EH038.10.01.04 L1 5720 SEA FILE=TOXCENTER 540-59-0 OR 156-59-2 OR 156-60-5 OR 25323-30-2 L2 5589 SEA FILE=TOXCENTER L1 NOT TSCATS/FS L3 4869 SEA FILE=TOXCENTER L2 NOT PATENT/DT L4 340 SEA FILE=TOXCENTER L3 AND ED>20170501 ACT 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?)

Table B-2. Database Query Strings

Database search date	Query string
	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?)
	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 133 SEA FILE=TOXCENTER L4 AND L37
	L39 4 SEA FILE=TOXCENTER L38 AND MEDLINE/FS

Table B-2. Database Query Strings

Database search date	Query string
	L40 7 SEA FILE=TOXCENTER L38 AND BIOSIS/FS L41 122 SEA FILE=TOXCENTER L38 AND CAPLUS/FS L42 0 SEA FILE=TOXCENTER L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L43 131 DUP REM L39 L40 L41 (2 DUPLICATES REMOVED) D SCAN L43 L44 935 SEA FILE=TOXCENTER 25323-30-2 L45 924 SEA FILE=TOXCENTER L44 NOT TSCATS/FS L46 688 SEA FILE=TOXCENTER L45 NOT PATENT/DT L47 40 SEA FILE=TOXCENTER L46 AND ED>20170501 L48 13 SEA FILE=TOXCENTER L47 AND L37 L*** DEL 4 S L38 AND MEDLINE/FS L*** DEL 4 S L38 AND MEDLINE/FS L49 4 SEA FILE=TOXCENTER L43 L*** DEL 7 S L38 AND BIOSIS/FS L*** DEL 7 S L38 AND BIOSIS/FS L50 7 SEA FILE=TOXCENTER L43 L*** DEL 122 S L38 AND CAPLUS/FS L*** DEL 122 S L38 AND CAPLUS/FS L51 120 SEA FILE=TOXCENTER L43 L52 0 SEA FILE=TOXCENTER L48 NOT (L49 OR L50 OR L51)
05/2017	(FILE 'HOME' ENTERED AT 09:05:27 ON 05 APR 2017) FILE 'TOXCENTER' ENTERED AT 09:05:48 ON 05 APR 2017 CHARGED TO COST=EH011.13.01.01 L1 4437 SEA 540-59-0 OR 156-59-2 OR 156-60-5 L2 859 SEA 25323-30-2 L3 5208 SEA L1 OR L2 L4 5077 SEA L3 NOT TSCATS/FS L5 4442 SEA L4 NOT PATENT/DT L6 2662 SEA L5 AND PY>=1999 ACTIVATE TOXQUERY/Q --------- L7 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L8 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L9 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L10 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L11 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L12 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L13 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L14 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L15 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)

Table B-2. Database Query Strings

Database search date	Query string
	L16 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)
	L17 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
	L18 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
	L19 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L20 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L21 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L22 QUE (ENDOCRIN? AND DISRUPT?)
	L23 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L24 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L25 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L26 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L27 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L28 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L29 QUE (NEPHROTOX? OR HEPATOTOX?)
	L30 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L31 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L32 QUE L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 OR L30 OR L31
	L33 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?)
	L34 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L35 QUE L32 OR L33 OR L34
	L36 QUE (NONHUMAN MAMMALS)/ORGN
	L37 QUE L35 OR L36
	L38 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?)
	L39 QUE L37 OR L38

	L40 647 SEA L6 AND L39
	L41 36 SEA L40 AND MEDLINE/FS

Table B-2. Database Query Strings

Database search date	Query string
	L42 31 SEA L40 AND BIOSIS/FS L43 574 SEA L40 AND CAPLUS/FS L44 6 SEA L40 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L45 621 DUP REM L41 L42 L44 L43 (26 DUPLICATES REMOVED) L*** DEL 36 S L40 AND MEDLINE/FS L*** DEL 36 S L40 AND MEDLINE/FS L46 36 SEA L45 L*** DEL 31 S L40 AND BIOSIS/FS L*** DEL 31 S L40 AND BIOSIS/FS L47 30 SEA L45 L*** DEL 574 S L40 AND CAPLUS/FS L*** DEL 574 S L40 AND CAPLUS/FS L48 549 SEA L45 L*** DEL 6 S L40 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L*** DEL 6 S L40 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L49 6 SEA L45 L50 585 SEA (L46 OR L47 OR L48 OR L49) NOT MEDLINE/FS L51 510 SEA L50 NOT 25323-30-2 D SCAN L51 L52 75 SEA L50 NOT L51 D SCAN L52 (FILE 'HOME' ENTERED AT 11:02:51 ON 31 MAY 2017) FILE 'TOXCENTER' ENTERED AT 11:03:35 ON 31 MAY 2017 CHARGED TO COST=EH011.13.01.01 L1 5239 SEA 540-59-0 OR 156-59-2 OR 156-60-5 OR 25323-30-2 L2 5108 SEA L1 NOT TSCATS/FS L3 4469 SEA L2 NOT PATENT/DT L4 765 SEA L3 AND PY>=1994 AND PY<=1998 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

Table B-2. Database Query Strings

Database search date	Query string
	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?)
	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 190 SEA L4 AND L37
	L39 8 SEA L38 AND MEDLINE/FS
	L40 15 SEA L38 AND BIOSIS/FS
	L41 159 SEA L38 AND CAPLUS/FS

Table B-2. Database Query Strings

Database search date	Query string
	L42 8 SEA L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L43 170 DUP REM L39 L40 L42 L41 (20 DUPLICATES REMOVED) L*** DEL 8 S L38 AND MEDLINE/FS L*** DEL 8 S L38 AND MEDLINE/FS L44 8 SEA L43 L*** DEL 15 S L38 AND BIOSIS/FS L*** DEL 15 S L38 AND BIOSIS/FS L45 12 SEA L43 L*** DEL 159 S L38 AND CAPLUS/FS L*** DEL 159 S L38 AND CAPLUS/FS L46 143 SEA L43 L*** DEL 8 S L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L*** DEL 8 S L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L47 7 SEA L43 L48 162 SEA (L44 OR L45 OR L46 OR L47) NOT MEDLINE/FS D SCAN L48

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
10/2021	Compounds searched: 540-59-0; 156-59-2; 156-60-5; 25323-30-2
NTP	
10/2021	"540-59-0" "156-59-2" "156-60-5" "25323-30-2" "Dichloroethene" "Dichloroethylene" "Acetylene dichloride" "Dichloroethylenes"
NIH RePORTER	
05/2022	" Text Search: "1,2-DCE" OR "1,2-Dichlor-aethen" OR "1,2-Dichloroethene" OR "1,2-Dichloroethylene" OR "Acetylene dichloride" OR "Dichloro-1,2-ethylene" OR "Dioform" OR "sym-Dichloroethylene" OR "(Z)-1,2-Dichloroethene" OR "(Z)-1,2-Dichloroethylene" OR "Acetalyne dichloride" OR "cis-Acetylene dichloride " OR "cis-1,2-Dichloroethene" OR "cis-1,2-Dichloroethylene" OR "cis-Dichloroethylene" OR "HCC 1130c" OR "R 1130c" OR "(1Z)-1,2-dichloro-Ethene " OR "1,2-Dichloroethylene" OR "(E)-1,2-Dichloroethene" OR "(E)-1,2-Dichloroethylene" OR "HCC 1130t" OR "R 1130t" OR "trans-1,2-Dichloroethene" OR "trans-1,2-Dichloroethylene" OR "trans-Acetylene dichloride" OR "trans-Dichloroethylene" OR "(1E)-1,2-dichloro-Ethene" OR "1,2-Dichloroethylene" OR "1,2-trans-Dichloroethylene" (advanced) " Limit to: Project Title, Project Terms, Project Abstracts
Other	Identified throughout the assessment process

The 2021 results were:

- Number of records identified from PubMed, Toxline, NTRL, and TOXCENTER (after duplicate removal): 1,873
- Number of records identified from other strategies: 99
- Total number of records to undergo literature screening: 1,972

B.1.2 Literature Screening

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

- 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.

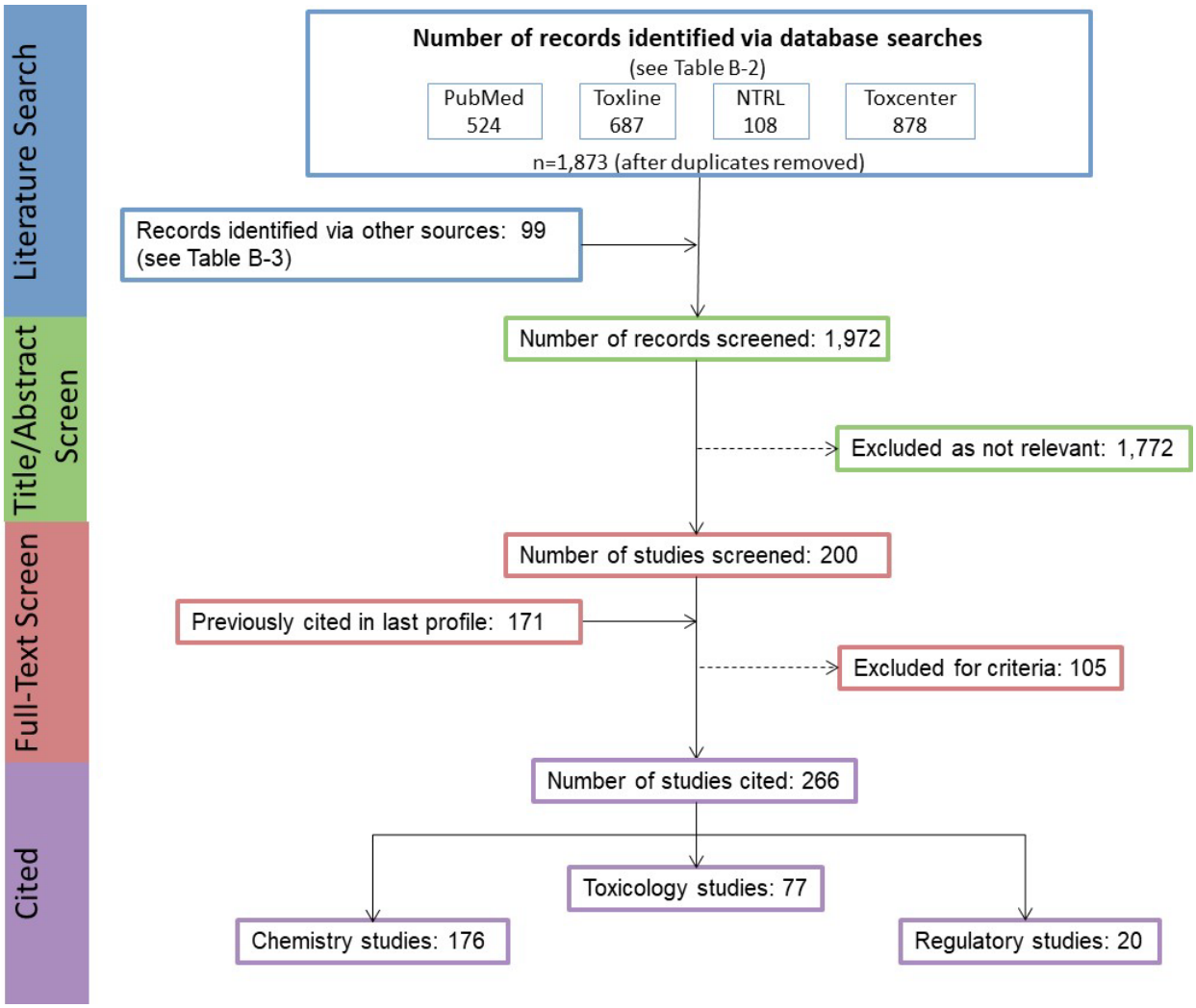
- Number of titles and abstracts screened: 1,972
- Number of studies considered relevant and moved to the next step: 200

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: 200
- Number of studies cited in the previous toxicological profile: 171
- Total number of studies cited in the profile: 266

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

Figure B-1. October 2021 Literature Search Results and Screen for 1,2-Dichloroethene



APPENDIX C. FRAMEWORK FOR ATSDR'S SYSTEMATIC REVIEW OF HEALTH EFFECTS DATA FOR 1,2-DICHLOROETHENE

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 1,2-dichloroethene, 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 1,2-dichloroethene:

- 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 1,2-dichloroethene. The inclusion criteria used to identify relevant studies examining the health effects of 1,2-dichloroethene are presented in Table C-1.

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

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

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

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

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

C.2. LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

A literature search and screen were conducted to identify studies examining the health effects of 1,2-dichloroethene. The literature search framework for the toxicological profile is discussed in detail in Appendix B.

C.2.1. Literature Search

As noted in Appendix B, the current literature search was intended to update the 1996 toxicological profile for 1,2-dichloroethene; thus, the literature search was restricted to studies published between January 1994 and October 2021. See Appendix B for the databases searched and the search strategy.

A total of 1,972 records relevant to all sections of the toxicological profile were identified (after duplicate removal).

C.2.2. Literature Screening

As described in Appendix B, a two-step process was used to screen the literature search to identify relevant studies examining the health effects of 1,2-dichloroethene.

Title and Abstract Screen. In the Title and Abstract Screen step, 1,972 records were reviewed; 7 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 22 health effect documents (documents identified in the update literature search and documents cited in older versions of the profile) was performed. From those 22 documents (43 studies), 5 documents (6 studies) were included in the qualitative review.

C.3 EXTRACT DATA FROM HEALTH EFFECTS STUDIES

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

Table C-2. Data Extracted From Individual Studies

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

A summary of the extracted data for each study is presented in the Supplemental Document for 1,2-dichloroethene and overviews of the results of the inhalation, oral, and dermal exposure studies are presented in Sections 2.2–2.18 of the profile and in the Levels Significant Exposures tables in Section 2.1 of the profile (Tables 2-1 through 2-5, respectively).

C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

Overviews of the potential health effect outcomes for 1,2-dichloroethene identified in human and animal studies are presented in Tables C-3 and C-4, respectively. The available human studies examined a limited range of effects; one study reported hepatic effects resulting from exposure to trans-1,2-dichloroethene. Animal studies examined several endpoints following inhalation, oral, or dermal exposure. The oral exposure studies examined most endpoints and reported body weight, hematological, ocular, dermal, immunological, neurological, and developmental. Of these effects, ocular and immunological were considered sensitive outcomes (i.e., effects were observed at low concentrations or doses). Studies examining these potential outcomes were carried through to Steps 4–8 of the systematic review. There were 6 studies (published in 5 documents) examining these potential outcomes carried through to Steps 4–8 of the systematic review.

APPENDIX C

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

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

APPENDIX C

Table C-4. Overview of the Health Outcomes for trans-1,2-Dichloroethene 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	1	2	2		1	2	2	2		1		2	1		1		
	1	2	1		1		2			1			1		1		
Intermediate-duration	1	2	2	1	1	2	2	2	1	1	1	2	1	1		1	
		1					1									1	
Chronic-duration																	
Oral studies																	
Acute-duration	2	1			3		3	1				3	1				
					1								1				
Intermediate-duration	4	2	2	2	2		4	4	2		2	4	2	3		2	
	1				1							1				1	
Chronic-duration																	
Dermal studies																	
Acute-duration	1								4	1							
	1								4	1							
Intermediate-duration																	
Chronic-duration																	

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

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

C.5 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES

C.5.1 Risk of Bias Assessment

The risk of bias of individual studies was assessed using OHAT's Risk of Bias Tool (NTP 2015). The risk of bias questions for animal experimental studies are presented in Table C-5. 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 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 animal experimental studies are presented in Table C-6.

APPENDIX C

Table C-6. Summary of Risk of Bias Assessment for trans-1,2-Dichloroethene—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	**Is there confidence in the outcome assessment?***	Were all measured outcomes reported?	Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Outcome: Ocular Effects										
Inhalation acute exposure										
Hurtt et al. 1993 (10-day)	++	+	+	+	++	+	+	++	na	First
Inhalation intermediate exposure										
DuPont 1998 (90-day)	++	+	++	+	++	++	+	++	na	First
Dermal (instillation into eye)										
DuPont 1988c	–	+	+	+	+	+	+	+	na	First
Outcome: Immune Effects (oral only)										
Oral acute exposure										
Munson et al. 1982 (14-day gavage)	–	+	–	+	+	–	++	+	na	First
Shopp et al. 1985 (14-day gavage)	–	+	+	+	+	+	++	+	na	First
Oral intermediate exposure										
Shopp et al. 1985 (90-day drinking water)	–	+	+	+	+	+	++	+	na	First

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

*Key question used to assign risk of bias tier

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

Confidences in the bodies of human and animal evidence were evaluated independently for each potential outcome. ATSDR did not evaluate the confidence in the body of evidence for carcinogenicity; rather, the Agency defaulted to the cancer weight-of-evidence assessment of other agencies including HHS, EPA, and IARC. The confidence in the body of evidence for an association or no association between exposure to trans-1,2-dichloroethene 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 vinyl acetate and a particular outcome was given an initial confidence rating based on the key features of the individual studies examining that outcome. The presence of these key features of study design was determined for individual studies using four "yes or no" questions, which were customized for epidemiology, human controlled exposure, or experimental animal study designs. Separate questionnaires were completed for each outcome assessed in a study. The key features for experimental animal studies are presented in Table C-7. 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-7. 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 ocular and immune observed in animal experimental studies are presented in Table C-8.

A summary of the initial confidence ratings for each outcome is presented in Table C-9. 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.

Table C-8. Presence of Key Features of Study Design for trans-1,2-Dichloroethene —Experimental Animal Studies

	Key feature				
Reference	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Outcome: Ocular Effects					
Inhalation acute exposure					
Hurtt et al. 1993 (10-day)	Yes	Yes	Yes	Yes	High
Inhalation intermediate exposure					
DuPont 1998 (90-day)	Yes	Yes	Yes	Yes	High
Dermal (instillation into eye)					
DuPont 1988c	No	No	Yes	No	Very low
Outcome: Immune Effects (oral only)					
Oral acute exposure					
Munson et al. 1982 (14-day gavage)	No	Yes	Yes	Yes	Moderate
Shopp et al. 1985 (14-day gavage)	Yes	Yes	Yes	Yes	High
Oral intermediate exposure					
Shopp et al. 1985 (90-day drinking water)	Yes	No	Yes	Yes	Moderate

Table C-9. Initial Confidence Rating for trans-1,2-Dichloroethene Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Ocular Effects		
Inhalation acute exposure		
Animal studies		
Hurtt et al. 1993 (10-day)	High	High
Inhalation intermediate exposure		
Animal studies		
DuPont 1998 (90-day)	High	High
Dermal acute exposure		
Animal studies		
DuPont 1988c	Very low	Very low
Outcome: Immune Effects (oral only)		
Oral acute exposure		
Animal studies		
Munson et al. 1982 (14-day gavage)	Moderate	High
Shopp et al. 1985 (14-day gavage)	High	
Oral intermediate exposure		
Animal studies		
Shopp et al. 1985 (90-day drinking water)	Moderate	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 ocular and immune effects are presented in Table C-10. If the confidence ratings for a particular outcome were based on more than one type of 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 1,2-dichloroethene exposure is presented in Table C-11.

Table C-10. Adjustments to the Initial Confidence in the Body of Evidence

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Outcome: Ocular effects			
Animal studies	High	-1 inconsistency in findings	Moderate
Outcome: Immune effects			
Animal studies	High	None	High

Table C-11. Confidence in the Body of Evidence for 1,2-Dichloroethene

	Confidence in body of evidence	
Outcome	Human studies	Animal studies
Ocular effects	None	Moderate
Immune effects	None	High

Five properties of the body of evidence were considered to determine whether the confidence rating should be downgraded:

- **Risk of bias.** Evaluation of whether there is substantial risk of bias across most of the studies examining the outcome. This evaluation used the risk of bias tier groupings for individual studies examining a particular outcome (Tables C-5 and C-6). 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 trans-1,2-dichloroethene, 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 trans-1,2-dichloroethene is presented in Table C-12.

Table C-12. Level of Evidence of Health Effects for trans-1,2-Dichloroethene

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Animal studies			
Ocular effects	Moderate	Health effect	Moderate
Immune effects	High	Health effect	High

C.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

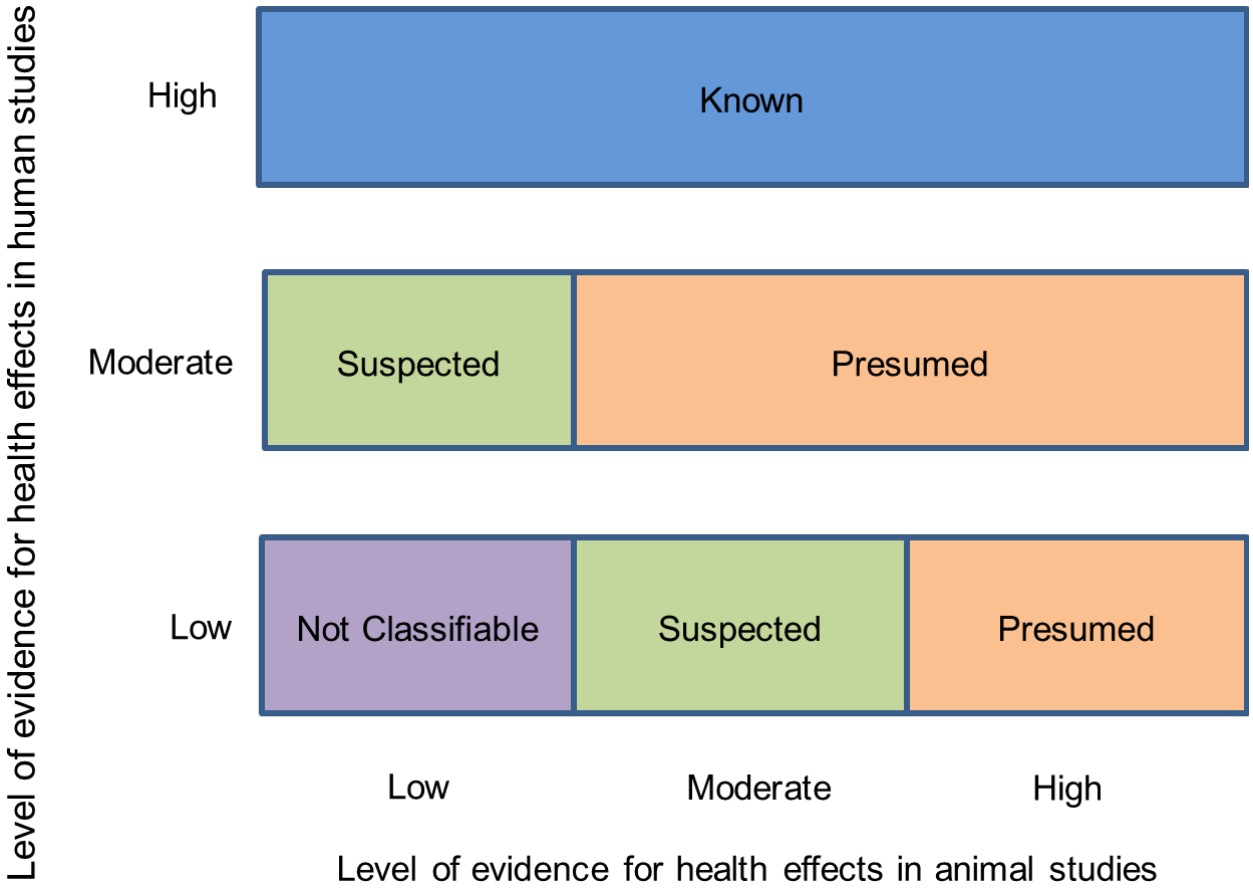
The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. For health effects, there were four hazard identification conclusion categories:

- **Known** to be a hazard to humans
- **Presumed** to be a hazard to humans
- **Suspected** to be a hazard to humans
- **Not classifiable** as to the hazard to humans

The initial hazard identification was based on the highest level of evidence in the human studies and the level of evidence in the animal studies; if there were no data for one evidence stream (human or animal), then the hazard identification was based on the one data stream (equivalent to treating the missing

evidence stream as having low level of evidence). The hazard identification scheme is presented in Figure C-1 and described below.

Figure C-1. Hazard Identification Scheme



- **Known:** A health effect in this category would have:
  - High level of evidence for health effects in human studies **AND** a high, moderate, or low level of evidence in animal studies.
- **Presumed:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** high or moderate level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** high level of evidence in animal studies
- **Suspected:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** low level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** moderate level of evidence in animal studies
- **Not classifiable:** A health effect in this category would have:
  - Low level of evidence in human studies **AND** low level of evidence in animal studies

Other relevant data such as mechanistic or mode-of-action data were considered to raise or lower the level of the hazard identification conclusion by providing information that supported or opposed biological plausibility.

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 trans-1,2-dichloroethene are listed below and summarized in Table C-13.

Table C-13. Hazard Identification Conclusions for trans-1,2-Dichloroethene

Outcome	Hazard identification
Ocular effects	Suspected
Immune effects	Presumed

Presumed Effects

- Immune effects
  - No human data.
  - High evidence of effects on humoral-mediated immunity following intermediate oral exposure (Shopp et al. 1985).

Suspected Effects

- Ocular effects
  - No human data.
  - Moderate evidence of ocular effects following acute inhalation exposure and eye instillation (DuPont 1988c; Hurtt et al. 1993).

APPENDIX D. USER'S GUIDE

Chapter 1. Relevance to Public Health

This chapter provides an overview of U.S. exposures, a summary of health effects based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information, and an overview of the minimal risk levels. This is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

Minimal Risk Levels (MRLs)

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

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Section 1.2, Summary of Health Effects, contains basic information known about the substance. Other sections, such as Section 3.2 Children and Other Populations that are Unusually Susceptible and Section 3.4 Interactions with Other Substances, provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a

substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables that are provided in Chapter 2. Detailed discussions of the MRLs are presented in Appendix A.

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species and MRLs to humans for noncancer endpoints. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE tables and figures follow. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

TABLE LEGEND

See Sample LSE Table (page D-5)

(1) Route of exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically, when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure (i.e., inhalation, oral, and dermal). LSE figures are limited to the inhalation and oral routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures. Profiles with more than one chemical may have more LSE tables and figures.

(2) Exposure period. Three exposure periods—acute (<15 days), intermediate (15–364 days), and chronic (≥365 days)—are presented within each relevant route of exposure. In this example, two oral studies of chronic-duration exposure are reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Figure key. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 51 identified NOAELs and less serious LOAELs (also see the three "51R" data points in sample LSE Figure 2-X).

(4) Species (strain) No./group. The test species (and strain), whether animal or human, are identified in this column. The column also contains information on the number of subjects and sex per group. Chapter 1, Relevance to Public Health, covers the relevance of animal data to human toxicity and Section 3.1, Toxicokinetics, contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(5) Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 51), rats were orally exposed to “Chemical X” via feed for 2 years. For a

more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Aida et al. 1992).

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), food intake (FI), gross necropsy (GN), hematology (HE), histopathology (HP), immune function (IX), lethality (LE), neurological function (NX), organ function (OF), ophthalmology (OP), organ weight (OW), reproductive function (RX), urinalysis (UR), and water intake (WI).

(7) Endpoint. This column lists the endpoint examined. The major categories of health endpoints included in LSE tables and figures are death, body weight, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, developmental, other noncancer, and cancer. "Other noncancer" refers to any effect (e.g., alterations in blood glucose levels) not covered in these systems. In the example of key number 51, three endpoints (body weight, hematological, and hepatic) were investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. The body weight effect reported in key number 51 is a NOAEL at 25.5 mg/kg/day. NOAELs are not reported for cancer and death; with the exception of these two endpoints, this field is left blank if no NOAEL was identified in the study.

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. Key number 51 reports a less serious LOAEL of 6.1 mg/kg/day for the hepatic system, which was used to derive a chronic exposure, oral MRL of 0.008 mg/kg/day (see footnote "c"). MRLs are not derived from serious LOAELs. A cancer effect level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases. If no LOAEL/CEL values were identified in the study, this field is left blank.

(10) Reference. The complete reference citation is provided in Chapter 8 of the profile.

(11) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. For example, footnote "c" indicates that the LOAEL of 6.1 mg/kg/day in key number 51 was used to derive an oral MRL of 0.008 mg/kg/day.

FIGURE LEGEND

See Sample LSE Figure (page D-6)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(12) Exposure period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the chronic exposure period are illustrated.

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

(14) Levels of exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(15) LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).

(16) CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.

(17) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral (1)

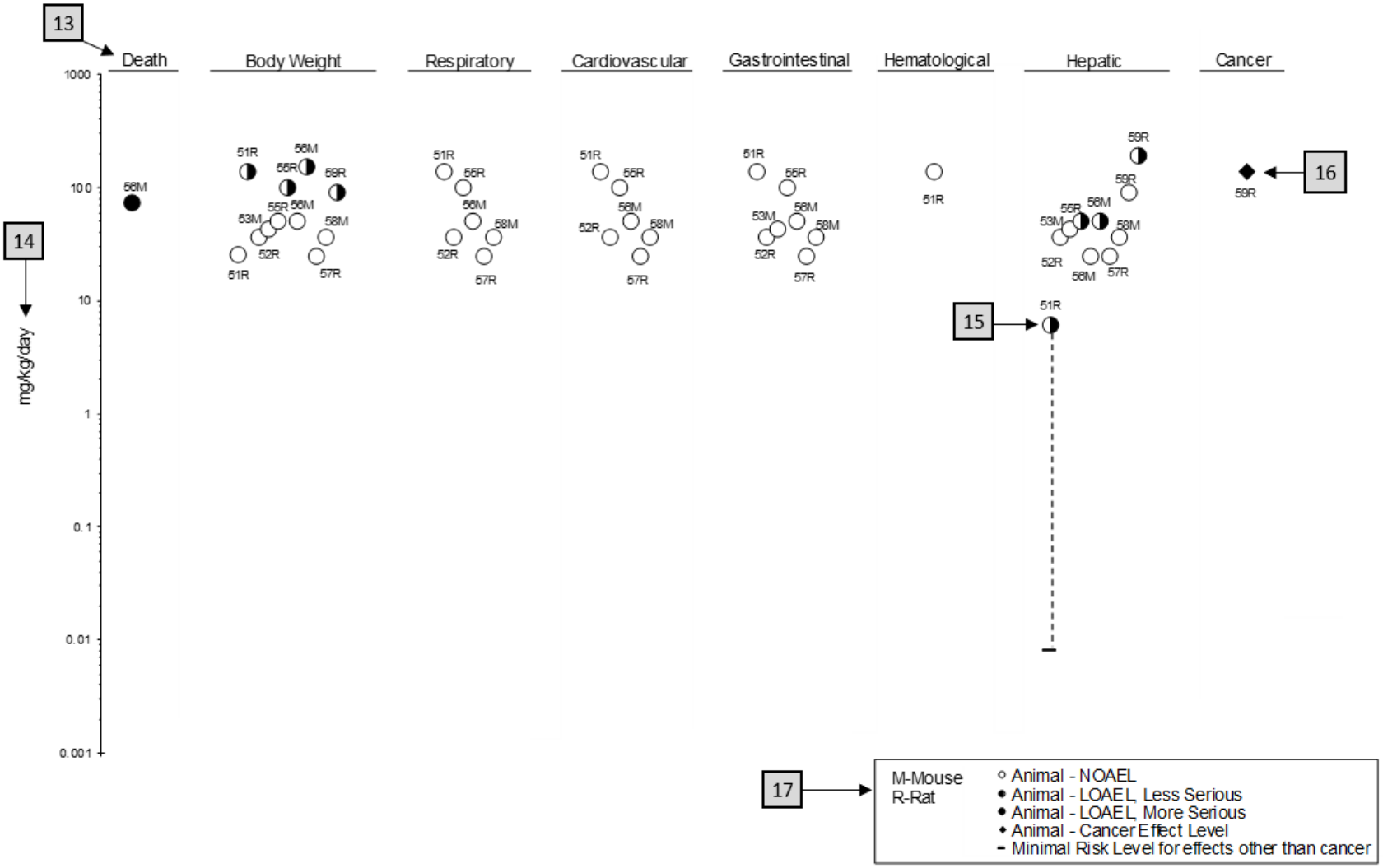
Figure key[a] (3)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 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

ATSDR develops educational and informational materials for health care providers categorized by hazardous substance, clinical condition, and/or by susceptible population. The following additional materials are available online:

Physician Briefs discuss health effects and approaches to patient management in a brief/factsheet style. *Physician Overviews* are narrated PowerPoint presentations with Continuing Education credit available (see https://www.atsdr.cdc.gov/emes/health_professionals/index.html).

Managing Hazardous Materials Incidents is a set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.html).

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: https://www.cdc.gov/nceh/.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: https://www.niehs.nih.gov/.

Clinical Resources (Publicly Available Information)

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

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

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

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

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

APPENDIX F. GLOSSARY

Absorption—The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to the taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of ≤14 days, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD) or Benchmark Concentration (BMC)—is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a BMD_{10} would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

Cancer Effect Level (CEL)—The lowest dose of a chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical or agent 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	lactate dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Level of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
MRL	Minimal Risk Level
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
Mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NCEH	National Center for Environmental Health
ND	not detected
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences

NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEHSU	Pediatric Environmental Health Specialty Unit
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure 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
SLOAEL	serious lowest-observed-adverse-effect level
SMR	standardized mortality ratio
sRBC	sheep red blood cell
STEL	short term exposure limit
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey

USNRC	U.S. Nuclear Regulatory Commission
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result