Toxicological Profile for 1,1-Dichloroethene

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

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DISCLAIMER

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FOREWORD

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

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

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

Each profile includes the following:

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

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

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

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

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

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*Legislative Background

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

VERSION HISTORY

Date	Description
April 2022	Final toxicological profile released
December 2019	Draft for public comment toxicological profile released
July 2009	Addendum to the toxicological profile released
May 1994	Final toxicological profile released
December 1990	Final toxicological profile released

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

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

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

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

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CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

1,1-Dichloroethene (Chemical Abstracts Service [CAS] Registry Number 75-35-4; synonyms include 1,1-dichloroethylene and vinylidene chloride) is a human-made chemical that does not occur naturally in the environment. The major use for 1,1-dichloroethene is as a chemical intermediate to make other products. 1,1-Dichloroethene is used to make various plastics, such as packaging materials and flexible films and as flame retardant coatings for fiber and carpet backing. 1,1-Dichloroethene is a colorless liquid that evaporates quickly at room temperature, has a mild, sweet smell, is flammable, and burns quickly.

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

1.2 SUMMARY OF HEALTH EFFECTS

Information on the toxicity of 1,1-dichloroethene primarily comes from studies conducted in experimental animals. Three limited studies evaluated the toxicity of 1,1-dichloroethene in humans. Approximately 90 experiments conducted in animals were available for review. Two-thirds of the studies employed inhalation exposure; one-third of the studies employed oral exposure. Results from selected oral studies indicated species and sex differences in 1,1-dichloroethene toxicity, as well as differences related to nutritional status (i.e., fasted animals were more sensitive than fed animals). Limited information was available regarding 1,1-dichloroethene toxicity following dermal exposure. As illustrated in Figures 1-1 and 1-2, the most sensitive effects appear to be depressed body weight, nasal tissue damage, liver damage, kidney damage, and delayed skeletal development. A systematic review of respiratory, hepatic, and renal endpoints conducted by ATSDR resulted in the following hazard identification conclusions (see Appendix C for details):

- Upper respiratory tract toxicity is a presumed health effect for humans
- Liver toxicity is a presumed health effect for humans
- Kidney toxicity is a presumed health effect for humans

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

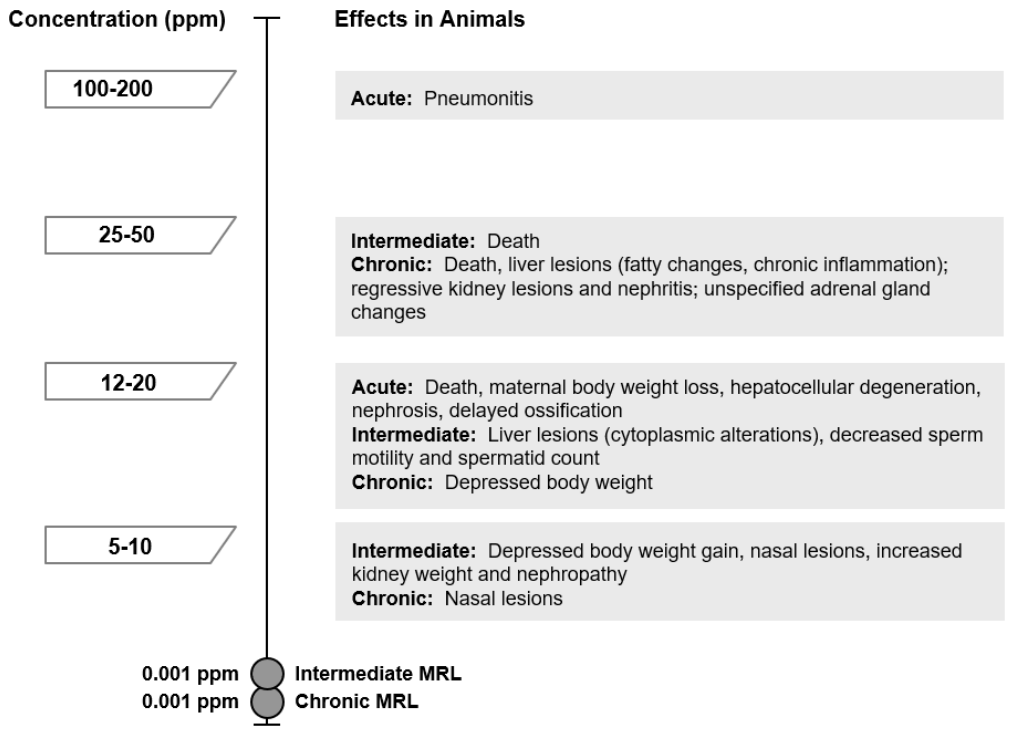
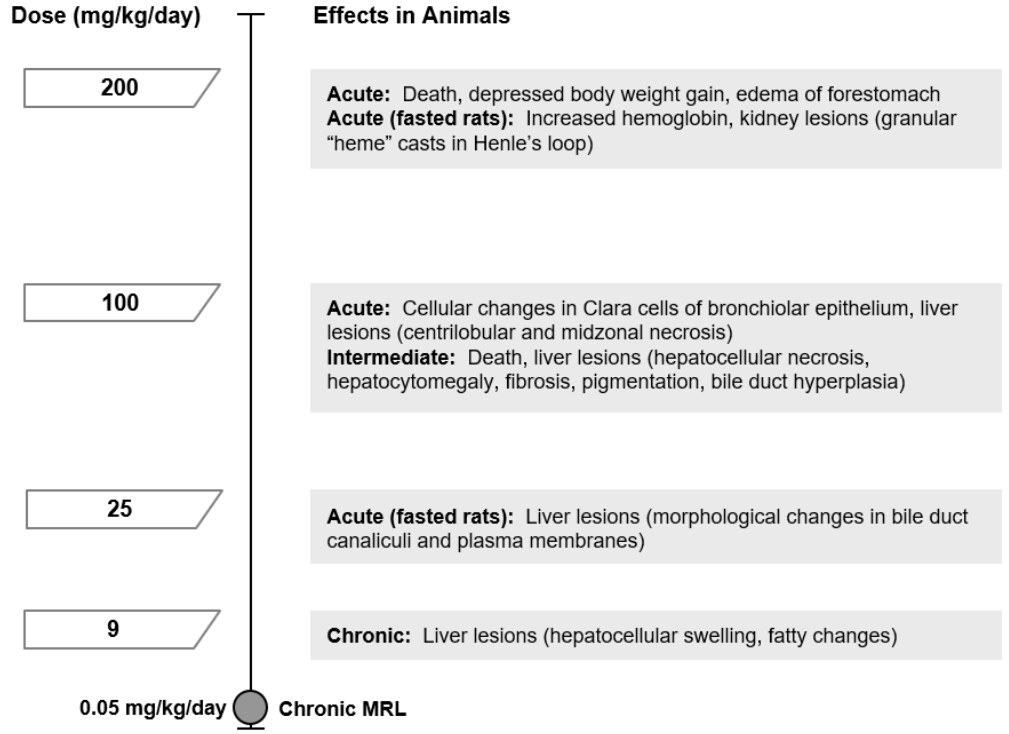


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to 1,1-Dichloroethene



Body Weight Effects. Depressed body weight or body weight loss were reported among maternal rats intermittently exposed to 1,1-dichloroethene vapor during major portions of gestation at exposure levels as low as 15–56 ppm (EPA 1977a) and rabbits exposed at 160 ppm (Murray et al. 1979). Adverse body weight effects were observed in other inhalation studies that employed repeated or continuous exposure of rats, mice, or rabbits at concentrations in the range of 6.25–500 ppm (Gage 1970; Henck et al. 1979; Maltoni et al. 1985; NTP 2015a; Prendergast et al. 1967).

In a series of oral studies of rats and mice repeatedly gavaged with 1,1-dichloroethene (NTP 1982), depressed body weight gain was noted in male rats treated for 14 days at 500 mg/kg/day and similarly treated female rats at 100 mg/kg/day. Depressed body weight gains were observed in male and female rats treated for 90 days at 250 mg/kg/day. There were no apparent treatment-related effects on body weight among similarly treated mice.

Respiratory Effects. Well-conducted inhalation studies in rats and mice support the identification of the upper respiratory system as a presumed target in humans. Effects in animals exposed to 1,1-dichloroethene by inhalation include increased lung weight; chronic active inflammation; hyperostosis; nasal turbinate atrophy; and/or olfactory epithelial mineralization, necrosis, atrophy, and/or metaplasia at repeated exposure levels as low as 6.25–25 ppm (NTP 2015a). In intermediate-duration inhalation studies, rats appear to be more sensitive than mice. Single oral dosing of mice resulted in damage and disruption of Clara cells (club cells) in the lung and increased lung weight (Forkert et al. 1985).

Hepatic Effects. Results from inhalation and oral animal studies support the identification of the liver as a presumed target in humans. Animal studies identify the liver as a major target organ of 1,1-dichloroethene toxicity associated with acute-, intermediate-, and chronic-duration inhalation and oral routes of exposure. Hepatotoxicity is evident by the appearance of both biochemical changes such as alterations in serum enzyme levels indicative of liver injury and induction of hepatic enzymes (e.g., Jaeger 1977; Jaeger et al. 1974; Jenkins and Andersen 1978; Short et al. 1977d) and marked histological changes (e.g., midzonal and centrilobular swelling of liver, degeneration and necrosis of hepatocytes) (e.g., Henck et al. 1979; Jenkins and Andersen 1978; Maltoni et al. 1985; NTP 1982, 2015a). Acute-duration inhalation and oral studies have demonstrated that fasted animals are more susceptible than nonfasted animals to 1,1-dichloroethene hepatotoxicity.

Renal Effects. Results from inhalation and oral animal studies support the identification of the kidney as a presumed target in humans. Adverse effects have been observed in the kidneys of experimental animals

following acute-, intermediate-, and chronic-duration inhalation exposure to 1,1-dichloroethene. These effects are manifested as enzyme changes (decreases in kidney monooxygenase and epoxide hydrolase levels) (Oesch et al. 1983), tubular alterations (hemoglobinuria) (McKenna et al. 1978a), increased kidney weight (Henck et al. 1979; NTP 2015a; Quast et al. 1986), and histological changes (nephropathy; tubular swelling, degeneration, and necrosis; granular casts in renal tubules of males) (e.g., Jackson and Conolly 1985; NTP 2015a; Short et al. 1977a). Male mice appear to be more susceptible than female mice to the acute nephrotoxic effects of inhaled 1,1-dichloroethene and more susceptible than both sexes of rats. Acute-duration inhalation and oral studies have demonstrated that fasted animals are more susceptible than nonfasted animals to 1,1-dichloroethene renal toxicity.

Developmental Effects. Available human data are restricted to population-based, cross-sectional studies conducted in northern New Jersey for the years 1985–1988; these studies provide only suggestive evidence of impaired orofacial and nervous system development associated with total dichloroethylenes in public drinking water (Bove et al. 1995). Delayed ossification of selected bones was reported for fetuses from maternal mice exposed to 1,1-dichloroethene vapor during gestation (EPA 1977a).

Cancer. Limited human data have not found associations between exposure to 1,1-dichloroethene and risk of cancer. Only two studies (Ott et al. 1976; Waxweiler 1981) were available for analysis and neither study was large enough to demonstrate a relationship between cancer and 1,1-dichloroethene unless there was an overt causality.

The carcinogenicity of 1,1-dichloroethene following inhalation, oral, dermal, or subcutaneous exposure has been evaluated in mice (Hong et al. 1981; Lee et al. 1978; Maltoni et al. 1985; Van Duuren et al. 1979), rats (Hong et al. 1981; Maltoni et al. 1982, 1985; NTP 1982; Ponomarkov and Tomatis 1980; Quast et al. 1983, 1986; Rampy et al. 1977; Viola and Caputo 1977), and Chinese hamsters (Maltoni et al. 1985).

In a chronic toxicity/carcinogenicity study of rats that employed the inhalation exposure route, significantly increased incidences of malignant mesothelioma and nasal respiratory epithelium adenoma were observed in males and significantly increased incidences of C-cell tumors, mononuclear cell leukemia, and malignant mammary gland tumors were observed in females (NTP 2015a). In a study of mice intermittently exposed for 52 weeks, significantly increased incidences of tumors included kidney adenocarcinoma in males, pulmonary tumors in males and females, and mammary gland tumors in females (Maltoni et al. 1985).

Negative findings of various other inhalation studies may be partially explained by inadequate test conditions. Study limitations for many of these investigations included less-than-lifetime exposure, use of concentrations well below or above the maximum tolerated dose, small numbers of animals, and/or limited gross or microscopic examinations (Hong et al. 1981; Lee et al. 1977, 1978; Maltoni et al. 1982, 1985; Quast et al. 1986; Rampy et al. 1977; Viola and Caputo 1977).

1,1-Dichloroethene was inactive as a complete carcinogen upon repeated application to the skin of mice for a lifetime and did not induce local malignancies when administered chronically by subcutaneous injection. However, a statistically significant increase in the incidence of skin papillomas was noted in Swiss mice treated dermally initially with 1,1-dichloroethene and subsequently with the tumor-promoting agent, phorbol myristate acetate (Van Duuren et al. 1979).

Several chronic studies in rats and mice evaluated the potential carcinogenicity of 1,1-dichloroethene by oral exposure. Administration was by gavage (Maltoni et al. 1982, 1985; NTP 1982; Ponomarkov and Tomatis 1980) or via the drinking water (Quast et al. 1983; Rampy et al. 1977). Trends toward increased incidences of malignant and nonmalignant tumors in 1,1-dichloroethene-treated animals were reported in some oral studies, although incidences for most tumor types were not statistically significantly increased by pairwise comparison (NTP 1982; Ponomarkov and Tomatis 1980; Quast et al. 1983).

1,1-Dichloroethene (vinylidene chloride) is not listed in the 14th Report on Carcinogens (NTP 2016). EPA (2002) reviewed available human and animal data and concluded that 1,1-dichloroethene "exhibits *suggestive evidence* of carcinogenicity but not sufficient evidence to assess human carcinogenic potential following inhalation exposure in studies of rodents." EPA (2002) also noted "the data for 1,1-dichloroethene are *inadequate* for an assessment of human carcinogenic potential by the oral route." IARC recently assigned 1,1-dichloroethene to Group 2B, based on "sufficient evidence of carcinogenicity in experimental animals" and no data or "inadequate evidence" in humans (Grosse et al. 2017).

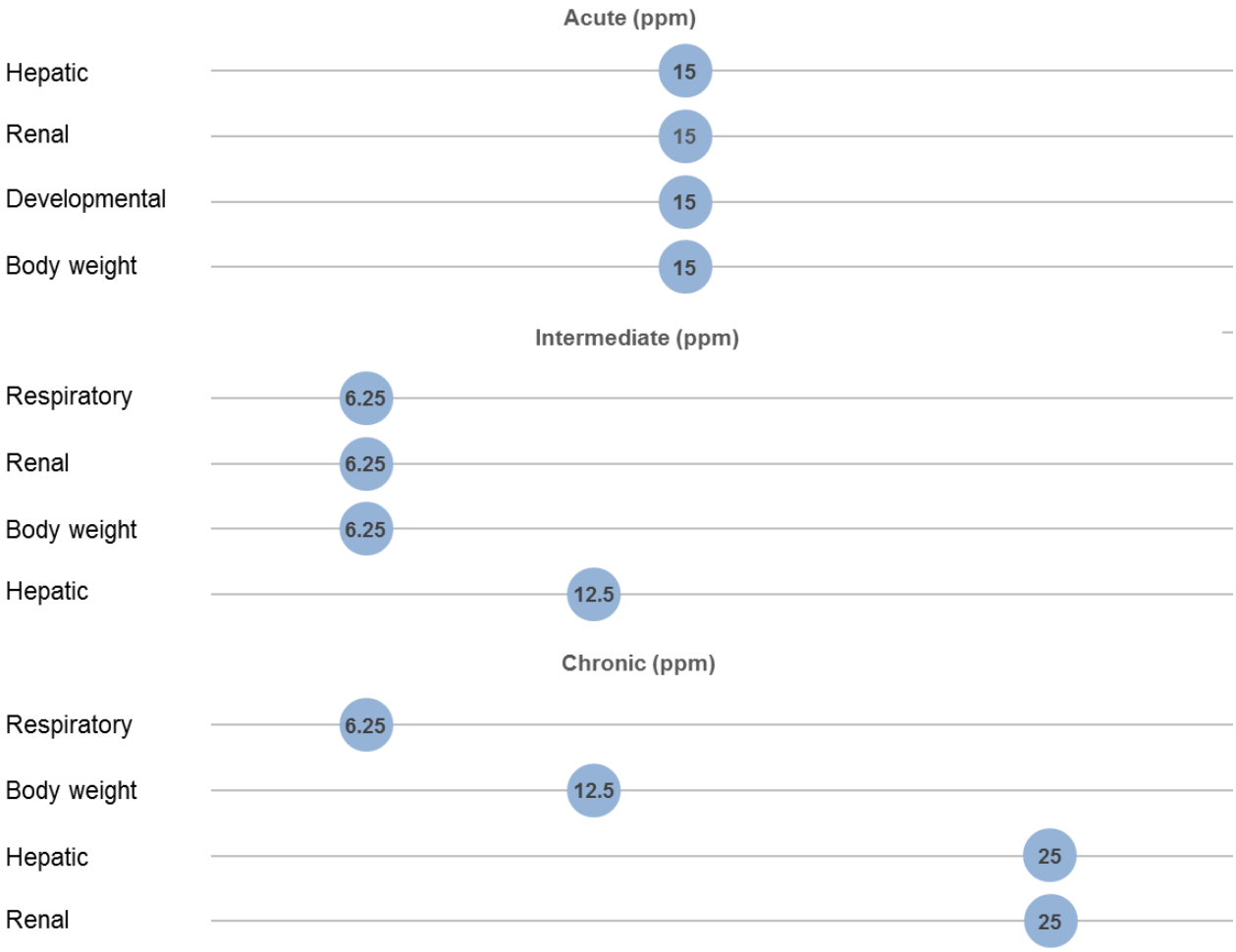
1.3 MINIMAL RISK LEVELS (MRLs)

The inhalation database was considered adequate for derivation of intermediate- and chronic-duration inhalation MRLs for 1,1-dichloroethene. As discussed in Appendix A, the inhalation database was not considered adequate for derivation of an acute-duration inhalation MRL. As presented in Figure 1-3, the available inhalation data for 1,1-dichloroethene suggest that the respiratory tract, liver, and kidney are sensitive targets of toxicity following inhalation exposure.

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

The upper respiratory tract and kidney are the most sensitive targets of 1,1-dichloroethene inhalation exposure.

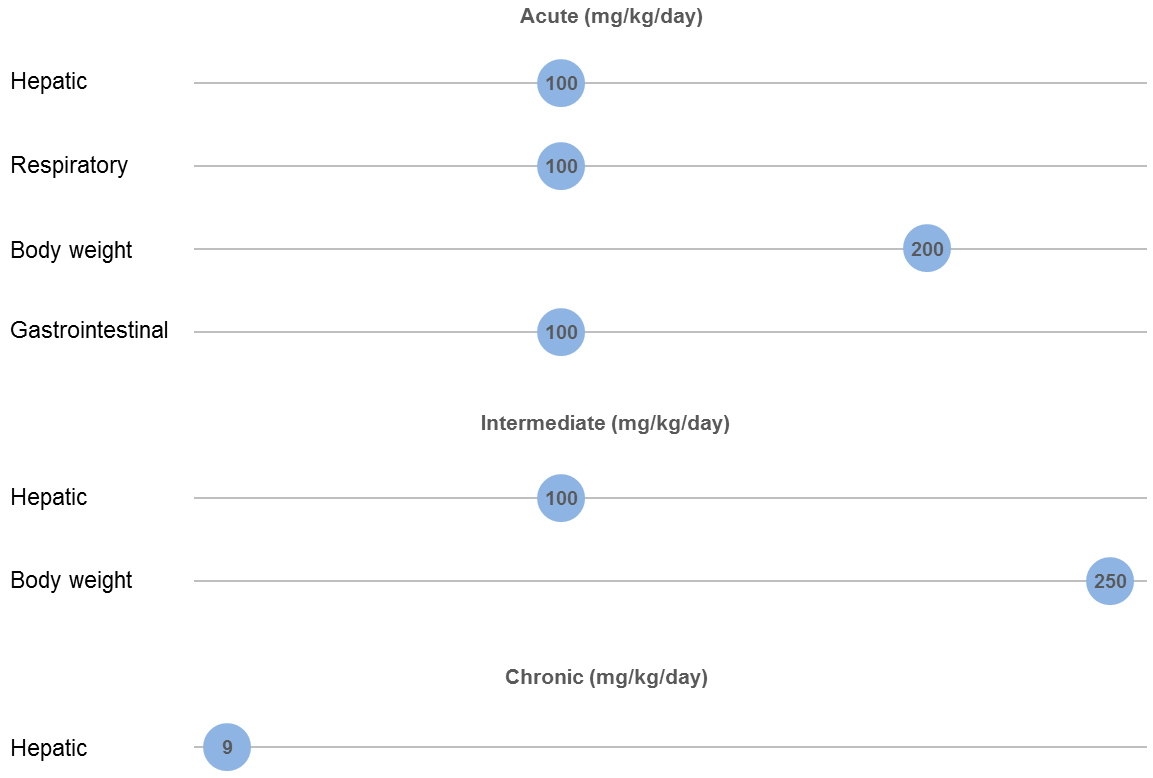
Numbers in circles are the lowest LOAELs for all health effects in animals; no exposure-response human data were identified.



The oral database was considered adequate for derivation of a chronic-duration oral MRL for 1,1-dichloroethene. The data were not considered adequate for derivation of acute- or intermediate-duration oral MRLs. As presented in Figure 1-4, the liver is the most sensitive target of toxicity following oral exposure.

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

The liver is the most sensitive target of 1,1-dichloroethene oral exposure.
Numbers in circles are the lowest LOAELs for all health effects in animals; no reliable dose-response data were available for humans.



The MRL values for 1,1-dichloroethene are summarized in Table 1-1 and discussed in greater detail in Appendix A.

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

Exposure duration	MRL	Critical effect	Point of departure/ human equivalent concentration	Uncertainty factor	Reference
Inhalation exposure (ppm)					
Acute	Insufficient data for MRL derivation				
Intermediate	0.001 (1 ppb)	Nasal olfactory epithelium necrosis	$BMCL_{10}$: 1.59 ($BMCL_{HEC}$: 0.036)	30	NTP 2015a
Chronic	0.001 (1 ppb)	Intermediate inhalation MRL adopted for chronic inhalation MRL			
Oral exposure (mg/kg/day)					
Acute	Insufficient data for MRL derivation				
Intermediate	Insufficient data for MRL derivation				
Chronic	0.05	Hepatic midzonal fatty change	$BMDL_{10}$: 4.51	100	Humiston et al. 1978; Quast et al. 1983

[a]See Appendix A for additional information.

$BMCL_{10}$ = upper 95% confidence limit on the benchmark concentration (BMC) associated with benchmark response rate of 10%; $BMDL_{10}$ = upper 95% confidence limit on the benchmark dose (BMD) associated with benchmark response rate of 10%; HEC = human equivalent concentration.

CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of 1,1-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. Figure 2-1 provides an overview of the database of studies in humans or experimental animals included in this chapter of the profile. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to 1,1-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 1,1-dichloroethene was also conducted; the results of this review are presented in Appendix C.

Animal inhalation studies are presented in Table 2-1 and Figure 2-2, and animal oral studies are presented in Table 2-2 and Figure 2-3; limited dermal data were identified for 1,1-dichloroethene.

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 (LOAELs) are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR

acknowledges that a considerable amount of judgment may be required in establishing whether an endpoint should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these endpoints. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health. Levels of exposure associated with cancer (Cancer Effect Levels, CELs) of 1,1-dichloroethene are indicated in Table 2-1 and Figure 2-2.

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.

Available information regarding the health effects of 1,1-dichloroethene derives almost exclusively from studies of experimental animals. As illustrated in Figure 2-1, approximately two-thirds of the studies employed inhalation exposure; only limited information is available for the dermal exposure route. The most examined endpoints in inhalation and oral studies were body weight, respiratory, hepatic, and renal. Based on animal data, the following targets of 1,1-dichloroethene were identified:

- **Body weight:** Depressed body weight or depressed body weight gain and actual body weight loss have been reported following inhalation or oral exposure of laboratory animals.

- **Respiratory endpoints:** Upper respiratory tract toxicity is a presumed health effect for humans based on strong evidence in animals. Increased lung weight, nasal lesions (e.g., hyperostosis, chronic active inflammation, metaplasia and atrophy in olfactory epithelium, hyperplasia in respiratory epithelium, turbinate atrophy), and laryngeal lesions (respiratory epithelial necrosis, metaplasia, and hyperplasia) have been associated with repeated inhalation exposure of rats and/or mice to 1,1-dichloroethene vapor. Clara cell (club cell) damage in the lungs was observed following oral exposure to 1,1-dichloroethene.

- **Hepatic endpoints:** Liver toxicity is a presumed health effect for humans based on strong evidence in animals. 1,1-Dichloroethene-induced liver effects, evidenced by biochemical changes (e.g., increases in serum liver enzyme levels, induction of hepatic enzymes) and marked histological changes (e.g., hepatocellular swelling, degeneration and necrosis of hepatocytes), have been reported in rats and mice for both inhalation and oral exposure routes. Fasting increases the hepatotoxicity of 1,1-dichloroethene.

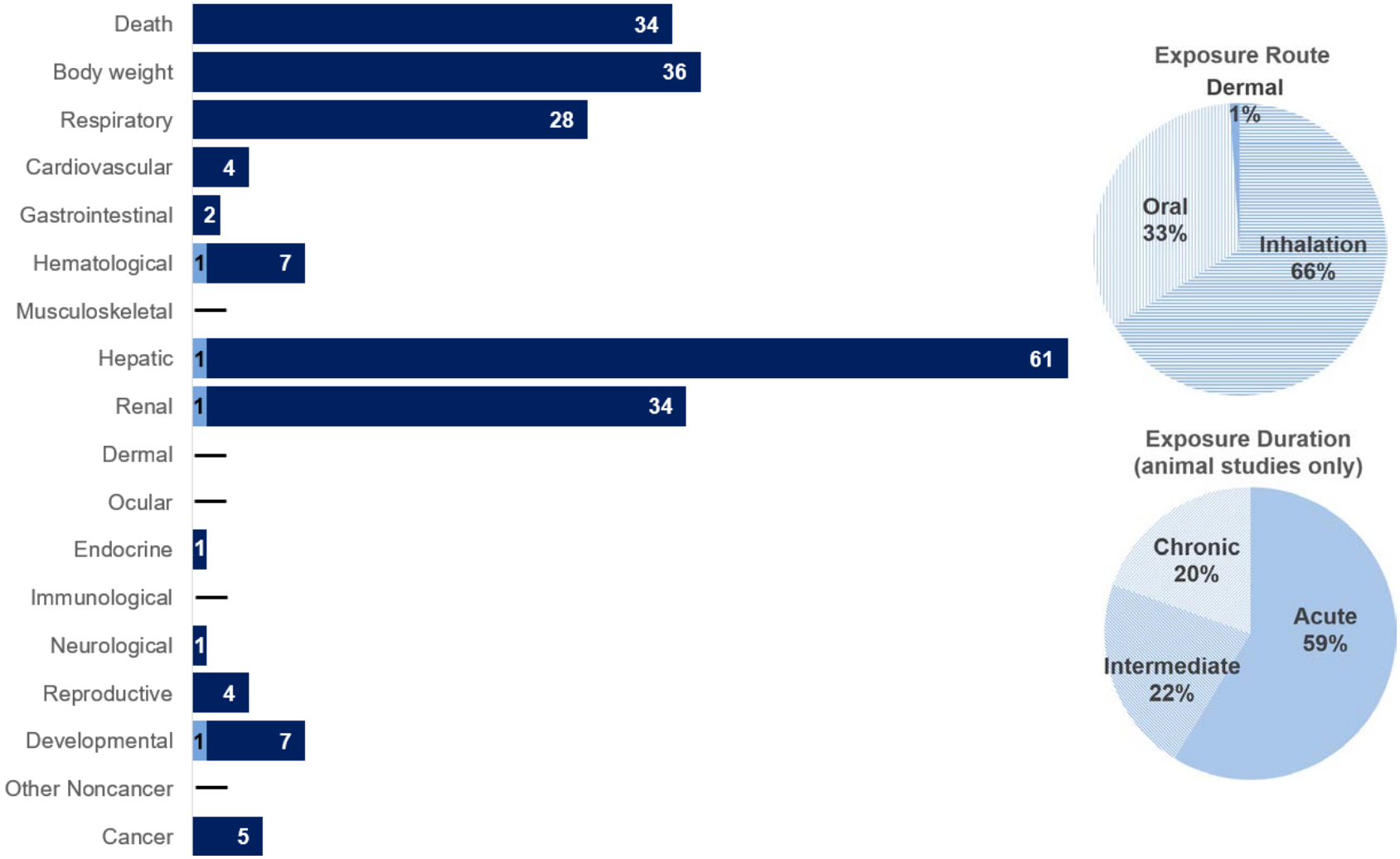
- **Renal endpoints:** Kidney toxicity is a presumed health effect for humans based on strong evidence in animals. 1,1-Dichloroethene-induced kidney effects, evidenced by increased kidney weight, enzyme changes (decreases in kidney monooxygenase and epoxide hydrolase levels), and histological changes (nephropathy and tubular swelling, degeneration, necrosis, and granular casts) were observed following repeated inhalation exposure; male mice appear to be most susceptible to 1,1-dichloroethene renal toxicity. Fasting increases renal toxicity.

- **Developmental endpoints:** Delayed ossification of selected bones was reported for fetuses from maternal mice exposed to 1,1-dichloroethene vapor during gestation.

- **Cancer:** Increased incidences of selected tumor types have been reported in some studies of rats or mice, most of which employed the inhalation exposure route. EPA (2002) considered available animal data to provide "*suggestive evidence* of carcinogenicity but not sufficient evidence to assess human carcinogenic potential following inhalation exposure" and "*inadequate* for an assessment of human carcinogenic potential by the oral route." IARC recently assigned 1,1-dichloroethene to Group 2B, based on "sufficient evidence of carcinogenicity in experimental animals" and no data or "inadequate evidence" in humans (Grosse et al. 2017).

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

Most studies examined the potential body weight, respiratory, liver, or kidney effects of 1,1-dichloroethene
More studies evaluated health effects in **animals** than in **humans** (counts represent studies examining endpoint)



*Includes studies discussed in Chapter 2. A total of 92 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

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

Figure Key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
ACUTE EXPOSURE									
1	Rat (CD) 19–24 F	GDs 8–20 22–23 hours/day	0, 56, 283	BH, BW, FX, LE, MX	Bd wt			56	Maternal body weight loss
EPA 1977a									
2	Rat (CD) 18–58 F	GDs 6–16 22–23 hours/day	0, 15, 57, 300, 449	BW, DX, FI, MX	Death			15	2/18 maternal rats died
					Bd wt			15	Maternal body weight loss
EPA 1977a									
3	Rat (Sprague-Dawley) 4–22 M	Once 4 hours	0, 200, 250, 300, 375, 400	BC, BW, HP, LE, OW	Renal		250		At 250 ppm, swelling in renal cortex of fasted male rats At 300 ppm, cortical tubular necrosis of fasted male rats
Jackson and Conolly 1985									
4	Rat (Sprague-Dawley) 2–24 M	Once 4 hours	0, 250	BI	Hepatic		250		Decreased mitochondrial GSH
Jaeger 1977									
5	Rat (Holtzman) 5 M	Once 4 hours	0, 2,000	BI, CS, LE	Death			2,000	Death of 2/5 rats exposed during period of low GSH activity
					Hepatic		2,000		Increased serum alanine α-ketoglutarate transaminase activity
Jaeger et al. 1973a									
6	Rat (Holtzman) 5-6 M	Once 4 hours	Up to 20,000	EA, LE	Death			600	Fasted male rat LC_{50}
					Hepatic	100	150		Increased serum alanine α-ketoglutarate transaminase activity in fasted rats
Jaeger et al. 1974									

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

Figure Key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
7	Rat (Holtzman) 5–6 M	Once 4 hours	Up to 20,000	EA, LE	Death			15,000	Nonfasted male rat LC_{50}
					Hepatic		2,000		Increased serum alanine α-ketoglutarate transaminase activity in nonfasted rats
Jaeger et al. 1974									
8	Rat (Sprague-Dawley) 4 M	Once 6 hours	10, 200	BM, EX, HP, TM, UM	Hepatic			200	Centrilobular degeneration and necrosis in fasted rats; no effect in nonfasted rats
					Renal			200	Hemoglobinuria; tubular degeneration in fasted rats; no effect in nonfasted rats
McKenna et al. 1978a									
9	Rat (Sprague-Dawley) 30 F treated 21 F control	GDs 6–15 7 hours/day	0 or 80	BW, CS, DX, FI, MX, OW, WI	Bd wt	80			
					Hepatic	80			
					Develop		80		Increased incidence of wavy ribs and delayed ossification of the skull
Murray et al. 1979									
10	Rat (Sprague-Dawley) 30 F treated 18 F control	GDs 6–15 7 hours/day	0 or 160	BW, CS, DX, FI, MX, OW, WI	Bd wt	160			
					Hepatic	160			
					Develop		160		Wavy ribs and delayed ossification of skull and cervical vertebrae
Murray et al. 1979									
11	Rat (Sprague-Dawley) 44 F treated 47 F control	GDs 6–15 7 hours/day	0 or 20	BW, CS, DX, FI, MX, OW, WI	Bd wt	20			
					Develop	20			
Murray et al. 1979									
12	Rat (CD) 5 or 10 M	1–3 days 22–23 hours/day	0, 60	BW, EA, HP, LE, OF	Hepatic		60		Mild to moderate centrilobular degeneration and/or necrosis, mild bile duct hyperplasia
					Renal	60			
Short et al. 1977a, 1977b									

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

Figure Key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
13	Rat (NMRI) 16 M	Once 4 hours	4,900, 6,150	LE	Death			6,350	LC_{50}
Siegel et al. 1971									
14	Rat (albino) NS M	Once 10 minutes	25,600	OF	Cardio			25,600	Cardiac arrhythmias
Siletchnik and Carlson 1974									
15	Rat (Sprague-Dawley) 10 M	Once 4 hours	0, 2,000	BC, BI, HP, LE	Death			2,000	6/10 male rats died
Szabo et al. 1977									
16	Rat (Sprague-Dawley) 10 M, 10 F	Once 4 hours	2,000, 5,000, 9,000, 15,000	BW, CS, HP, LE	Death			7,145 M 10,275 F	LC_{50} LC_{50}
					Resp		2,000		Panting or gasping
					Neuro		2,000		At 2,000 ppm, apathy; at 9,000 ppm, narcosis
Zeller et al. 1979a									
17	Rat (Sprague-Dawley) 10 M, 10 F	Once 4 hours	100–12,000	LE	Death			415 M 6,545 F	Fasted LC_{50} Fasted LC_{50}
Zeller et al. 1979b									
18	Mouse (CD-1) 17–50 M	5 days 6 hours/day	0, 10, 30, 50	DX, MX	Repro	30			
Andersen et al. 1977									

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

Figure Key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
19	Mouse (Ha[ICR]) 10 M, 10 F	12 days 5 days/week 6 hours/day	0, 55, 100, 200	BC, BW, CS, GN, HP, OW	Death			200	6/10 males and 4/10 females died within the first 4 exposure days
					Bd wt	55 M 100 F	100 M		Up to 18% depressed mean body weight
					Resp	100			
					Hepatic	100 F	55 M		At ≥55 ppm, 20–24% increased mean relative liver weight Concentration-related increasing incidence and/or severity of liver lesions (centrilobular hepatocellular swelling and/or necrosis)
					Renal	100 F	55 M		At 55 ppm, 27% increased kidney weight; exposure concentration-related increasing severity of degenerative nephrosis
Henck et al. 1979									
20	Mouse (B6C3F1) 10 M, 10 F	12 days 5 days/week 6 hours/day	0, 55, 100, 200	BC, BW, CS, GN, HP, OW	Death			200	All males died within the first 3 exposure days; all females died after the first exposure period
					Bd wt	100			
					Resp	100			
					Hepatic	55	100		20% increased liver weight, centrilobular hepatocellular hypertrophy in males and females; accentuated lobular pattern, hepatocellular degeneration/necrosis in females
					Renal	100 F	55 M 200 F		27% increased kidney weight and exposure concentration-related increasing severity of degenerative nephrosis in males Degenerative nephrosis in 2/5 females
Henck et al. 1979									

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

Figure Key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
21	Mouse (CD-1) 10 M, 10 F	12 days 5 days/week 6 hours/day	0, 55, 100, 200	BC, BW, CS, GN, HP, OW	Death			200 M	All males died within the first 5 exposure days
					Bd wt	200 F		55 M	Up to 26% depressed body weight in males
					Resp	100			
					Hepatic	100 M 55 F	100 F	200 M	At 100 ppm, minimal accentuated lobular pattern and centrilobular hepatocellular hypertrophy with pleomorphism in 5/5 females At 200 ppm, severe necrosis/ degeneration in males and females
					Renal	100 F	200 F	55 M	At 55 ppm, moderate to severe degenerative nephrosis in 5/5 males At 200 ppm, degenerative nephrosis in 2/5 females
Henck et al. 1979									
22	Mouse (CF-W) 10 M, 10 F	12 days 5 days/week 6 hours/day	0, 55, 100, 200	BC, BW, CS, GN, HP, OW	Death			200 M	All male mice died within the first 5 exposure days
					Bd wt	100 M 200 F			
					Resp	100			
					Hepatic		55	200	At 55 ppm, centrilobular hepatocellular hypertrophy At 200 ppm, hepatocellular necrosis in 5/5 males (severe) and 5/5 females (severe in males; severity not specified in females)
					Renal	200 F	55 M	200 M	At 55 ppm, moderate severity of degenerative nephrosis in 5/5 males At 200 ppm, severe degenerative nephrosis in 5/5 males
Henck et al. 1979									

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

Figure Key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
23	Mouse (Multiple) 30 or 60 M 30 or 60 F	2 days 4 hours/day	0, 200	BW, CS, HP, LE	Death			200	By day 10 following exposures, high rates of mortality among male Swiss, Balb/c, and C57Bl mice, and male and female C3H mice; no mortality among female Swiss, Balb/c, or C57Bl mice
					Bd wt		200		Depressed body weight among Swiss and Balb/c male mice and C3H and C57Bl male and female mice (magnitude not specified)
					Hepatic		200 F		Unspecified histopathologic liver changes in C3H female mice
					Renal		200 F		Unspecified histopathologic renal changes in C3H female mice
Maltoni et al. 1985									
24	Mouse (Swiss-Webster) 5–50 M	1, 3, or 8 days 6 hours/day	0, 10, 50	EA, LE	Death			50	20–82% mortality (higher mortality rates for 8-day exposures)
Oesch et al. 1983									
25	Mouse (CD-1) 3–6 M	Once 6 hours	10, 50	HP	Hepatic	10	50		Centrilobular swelling
Reitz et al. 1980									
26	Mouse (CD-1) 15–65 F	GDs 6–16 22–23 hours/day	0, 15, 30, 57, 144, 300	BW, DX, FI, MX, LE	Develop		15		Unossified incus, incompletely ossified sternebrae
EPA 1977a									
27	Mouse (CD-1) NS M	2 days 22–23 hours/day	NS	LE	Death			35	2-day LC_{50}
Short et al. 1977a, 1977b									

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

Figure Key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
28	Mouse (CD-1) 4–10 M	1–5 days 22–23 hours/day	0, 15, 30, 60	BW, EA, HP, LE, OF	Death			60	Death of 8/10 mice after 2 days of exposures
					Hepatic		15		Liver lesions (predominantly hepatocellular degeneration), up to 4.4-fold increased AST and 6.3-fold increased ALT levels
					Renal			15	Renal lesions, predominantly severe tubular nephrosis as early as day 1; tubular regeneration after 5 exposure days
Short et al. 1977a, 1977b									
29	Mouse (CD-1) NS M, NS F	Once 23 hours	NS	LE	Death			98 M 105 F	LC_{50}
Short et al. 1977a, 1977b									
30	Mouse (NMRI) 10 M, 10 F	Once 4 hours	10, 20, 25, 50, 76, 101 126, 150	HP	Death			50 M 125 F	Fasted LC_{50}
Zeller et al. 1979c									
31	Hamster (Chinese) 10 M, 10 F	Once 4 hours	245-4,730	BW, CS, GN, HP, LE	Death			1,915 M 2,945 F	LC_{50}
Klimisch and Freisberg 1979a									
32	Hamster (Chinese) 10 M, 10 F	Once 4 hours	126-2,006	GN, CS	Death			150 M 455 F	Fasted LC_{50}
Klimisch and Freisberg 1979b									

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

Figure Key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
33	Rabbit (New Zealand) 22 F treated 16 F control	GDs 6–18 7 hours/day	0 or 80	BW, CS, DX, FI, MX, OW, WI	Bd wt	80			
					Hepatic	80			
					Develop	80			
Murray et al. 1979									
34	Rabbit (New Zealand) 18 F treated 16 F control	GDs 6–18 7 hours/day	0 or 160	BW, CS, DX, FI, MX, OW, WI	Bd wt			160	0% mean maternal body weight gain during GDs 6–28
					Hepatic	160			
					Develop			160	Fetal resorptions
Murray et al. 1979									
INTERMEDIATE EXPOSURE									
35	Monkey (Squirrel) 3, 9, or 21 NS	90 days continuous	0, 5, 15, 25, 48	BC, BW, CS, GN, HP	Death			25	2/3 died (treatment days 39 and 47)
					Hepatic	25	48		Fatty metamorphosis, focal necrosis, hemosiderin deposition, lymphocytic infiltration, bile duct proliferation, fibrosis, pseudo-lobule formation
Prendergast et al. 1967									
36	Rat (Sprague-Dawley) 20 M, 20 F	90 days 5 days/week 6 hours/day	0, 26.4, 72.7	BC, BW, CS, GN, HP, OW	Hepatic		26.4		Cytoplasmic vacuolization
Balmer et al. 1976									
37	Rat (Alderley Park) 4 M, 4 F	4 weeks 5 days/week 6 hours/day	0, 200, 500	BW, CS, HP	Bd wt	200	500		Retarded weight gain
					Resp		200		Slight nasal irritation
					Hepatic	200	500		Degeneration of liver cells
Gage 1970									

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

Figure Key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
38	Rat (Sprague-Dawley) 60–158 per sex	15 weeks 5 days/week, 4 hours/day (7 weeks) 7 hours/day (8 weeks)	0, 100	BW, CS, GN, HP, LE	Bd wt	100			
					Resp	100			
					Hepatic	100			
					Renal	100			
Maltoni et al. 1985									
39	Rat (F344/N) 5 M, 5 F	16 days 5 days/week 6 hours/day (+12 minutes)	0, 25, 50, 100, 200, 400	BW, CS, HP, LE, OW	Death			200	100% mortality by day 4
					Bd wt	100 M 50 F	100 F		15% depressed mean body weight gain in females
					Hepatic		25		Centrilobular cytoplasmic alterations in hepatocytes
					Renal		25		12–20% lower mean relative kidney weight
NTP 2015a									
40	Rat (F344/N) 10 M, 10 F	14 weeks 5 days/week 6 hours/day (+10 minutes)	0, 6.25, 12.5, 25, 50, 100	BC, BW, CS, HE, HP, LE, OF, OW	Bd wt	100			
					Resp		6.25[b,c]		Olfactory epithelium mineralization in males and females, olfactory epithelium atrophy in males ($BMCL_{10}$ = 1.59 ppm)
					Hepatic	6.25 M 25 F	12.5 M 50 F		Males: hepatic centrilobular cytoplasmic alterations Females: cytoplasmic vacuolization in hepatocytes
					Renal	100			
					Repro	50 M 100 F	100 M		5% decreased sperm motility, 15–16% decreased spermatid count
NTP 2015a									
41	Rat (black-hooded Wistar) 4 M	4 weeks continuous	0, 50	HP	Hepatic		50		Fatty changes and focal necrosis
Plummer et al. 1990									

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

Figure Key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
42	Rat (black-hooded Wistar) 4 M	4 weeks 5 days/week 6 hours/day	0, 270	HP	Hepatic		270		Coagulative necrosis and cell infiltrate
Plummer et al. 1990									
43	Rat (Long-Evans or Sprague-Dawley) 15 or 45 NS	90 days continuous	0, 5, 15, 25, 48	BC, BW, CS, GN, HP	Resp	48			
					Hepatic	25		48	Fatty metamorphosis, focal necrosis, hemosiderin deposition, lymphocytic infiltration, bile duct proliferation, fibrosis, pseudo-lobule formation
					Renal	25	48		Nuclear hypertrophy of tubular epithelium
Prendergast et al. 1967									
44	Rat (Sprague-Dawley) 8 M, 8 F	30 days 5 days/week 6 hours/day	0, 125, 200	BC, GN, HP, OW, UR	Hepatic		125	200	At 125 ppm, centrilobular and midzonal cytoplasmic vacuolization; at 200 ppm, necrosis
Quast 1976									
45	Rat (Sprague-Dawley) 5 M, 5 F	6 months 5 days/week 6 hours/day	0, 25, 75	BC, BW, CS, HE, HP, OW, UR	Resp	75			
					Hemato	75			
					Hepatic	25	75		Fatty changes in the midzonal region of the liver at 6-month sacrifice
Quast et al. 1986									
46	Rat (CD) 11 M	11 weeks 5 days/week 6 hours/day	0, 55	OF	Repro	55			
Short et al. 1977c									

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

Figure Key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
47	Mouse (B6C3F1/N) 5 M, 5 F	17 days 5 days/week 6 hours/day (+12 minutes)	0, 25, 50, 100, 200, 400	BW, CS, HP, LE, OW	Death			100 M 200 F	At ≥100 ppm, all males died At ≥200 ppm, all females died
					Bd wt	50 M 100 F			
					Resp		25 M 25 F	100 M 200 F	Males: at 25 ppm, 15% increased lung weight; at 100 ppm, respiratory epithelium necrosis Females: at 25 ppm, 36% increased lung weight; at 200 ppm, respiratory epithelium necrosis
					Hepatic		25		At 25 ppm, 10–14% increased relative liver weight; at 100 ppm, centrilobular necrosis
					Renal	100 F		25 M	Renal tubule necrosis and regeneration, granular casts in males
NTP 2015a									
48	Mouse (B6C3F1/N) 10 M, 10 F	14 weeks 5 days/week 6 hours/day (+10 minutes)	M: 0, 6.25, 12.5, 25, 50; F: 0, 6.25, 12.5, 25, 50, 100	BW, CS, GN, HP, LE	Death			50 M 100 F	2/10 males died during the first week 4/10 females died during the first week
					Bd wt	6.25 M		12.5 M 6.25 F	24–27% depressed mean body weight gain
					Resp	6.25	12.5		At 12.5 ppm, 12–16% increased relative lung weight; at 50 ppm, squamous metaplasia in laryngeal respiratory epithelium; at 100 ppm, laryngeal respiratory epithelial necrosis and hyperplasia in females
					Hepatic	50 M 50 F	100 F		Necrosis, hepatocellular hypertrophy in females
					Renal	6.25 M	12.5 M 6.25 F		Nephropathy in males, 11% increased relative kidney weight in females
					Repro	6.25 M 100 F	12.5 M		19% decreased epididymal sperm count
NTP 2015a									

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

Figure Key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
49	Guinea pig (Hartley) 15 or 45 NS	90 days continuous	0, 5, 15, 25, 48	BC, BW, CS, GN, HP	Resp	48			
					Hepatic	5	48		Increased serum ALT
Prendergast et al. 1967									
50	Dog (Beagle) 2 or 6 NS	90 days continuous	0, 5, 15, 25, 48	BC, BW, CS, GN, HP	Resp	48			
					Hepatic	25	48		Fatty metamorphosis, focal necrosis, hemosiderin deposition, lymphocytic infiltration, bile duct proliferation, fibrosis, pseudo-lobule formation
					Renal	48			
Prendergast et al. 1967									
CHRONIC EXPOSURE									
51	Rat (CD) 36 M, 36 F	Up to 12 months 5 days/week 6 hours/day	0, 55	BW, CS, FI, GN	Bd wt	55			
					Hemato	55			
					Hepatic		55		Mild to markedly severe focal, disseminated vacuolization (probably fatty change)
Lee et al. 1977, 1978									
52	Rat (Sprague-Dawley) 54–60 F; 61–158 M offspring	104 weeks 5 days/week 4 hours/day (7 weeks) 7 hours/day (97 weeks)	0, 100	BW, CS, GN, HP, LE	Bd wt	100			
					Resp	100			
					Hepatic	100			
					Renal	100			
Maltoni et al. 1985									
53	Rat (Sprague-Dawley) 30–100 M 30–100 F	52 weeks 5 days/week 4 hours/day	0, 10, 25, 50, 100, 150	BW, CS, GN, HP, LE	Bd wt	150			
					Resp	150			
					Hepatic	150			
					Renal	150			
Maltoni et al. 1985									

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

Figure Key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
54	Rat (F344/N) 50 M, 50 F	105 weeks 5 days/week 6 hours/day (+10 minutes)	0, 25, 50, 100	BW, CS, GN, HP, LE	Death			100 F	Decreased survival
					Bd wt	100			
					Resp		25		Turbinate atrophy and hyperostosis, olfactory epithelium metaplasia, chronic active inflammation in males and females, respiratory epithelium hyperplasia in males
					Hepatic		25		Chronic inflammation, diffuse fatty change
					Renal	100			
					Cancer			25 M 100 F	CEL: malignant mesothelioma in males, thyroid gland C-cell adenoma and adenoma or carcinoma combined; mononuclear cell leukemia in females
NTP 2015a									
55	Rat (Sprague-Dawley) 85 or 86 M 85 or 86 F (18 other rats/sex for interim sacrifices)	Up to 18 months 5 days/week 6 hours/day	0, 25, 75	BC, BW, CS, HE, HP, OW, UR	Bd wt	75			
					Resp	75			
					Hemato	75			
					Hepatic		25		Fatty changes in the midzonal region of the liver at 12-month sacrifice
					Renal	75			
Quast et al. 1986									
56	Mouse (CD-1) 36 M, 36 F	Up to 12 months 5 days/week 6 hours/day	0, 55	BW, CS, FI, GN	Bd wt	55			
					Hemato	55			
					Hepatic			55	Liver lesions including focal degeneration and necrosis
Lee et al. 1977, 1978									

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

Figure Key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
57	Mouse (Swiss) 30 M, 30 F (exposed) 100 M, 100 F (control)	52 weeks 5 days/week 4 hours/day	0, 10, 25	BW, CS, GN, HP, LE	Resp	25			
					Hepatic	25			
					Renal		25		Unspecified regressive nonneoplastic kidney lesions
					Cancer			10	CEL: pulmonary tumors; increased numbers of total tumors
Maltoni et al. 1985									
58	Mouse (Swiss) 120 M, 120 F (exposed) 90 M, 90 F (control)	52 weeks 4–5 days/week 4 hours/day	0, 25	BW, CS, GN, HP, LE	Resp	25 F	25 M		Bronchopneumonia in males
					Hepatic	25			
					Renal		25		Abscesses and nephritis
					Endocr		25		Unspecified adrenal gland changes
					Cancer			25	CEL: kidney adenocarcinoma in males, pulmonary tumors in males and females, mammary gland tumors in females
Maltoni et al. 1985									
59	Mouse (B6C3F1/N) 50 M, 50 F	105 weeks 5 days/week 6 hours/day (+10 minutes)	0, 6.25, 12.5, 25	BW, CS, GN, HP, LE	Death			25	Decreased survival
					Bd wt	6.25 M 12.5 F	12.5 M 25 F		11–12% depressed mean body weight in males, 14–20% depressed mean body weight in females
					Resp		6.25[c]		Nasal turbinate atrophy, hyperostosis, metaplasia of respiratory olfactory epithelium
					Hepatic	25			
					Renal	25 F	6.25 M		Increased incidence of renal tubule hyperplasia at ≥6.25 ppm; renal cysts at 25 ppm
					Cancer			6.25 M 12.5 F	CEL: Renal tubule adenoma, carcinoma, and adenoma or carcinoma combined in males; hepatocellular adenoma or carcinoma combined in females
NTP 2015a									

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

Figure Key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
60	Hamster (Chinese) 30 M, 30 F (exposed) 17 M, 18 F (control)	52 weeks 4–5 days/week 4 hours/day	0, 25	BW, CS, GN, HP, LE	Bd wt	25			
					Resp	25			
					Hepatic	25			
					Renal	25			
Maltoni et al. 1985									

[a]The number corresponds to entries in Figure 2-2; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-2. Where such differences exist, only the levels of effect for the most sensitive gender are presented.
[b]Used to derive an intermediate-duration inhalation minimal risk level (MRL) of 0.001 ppm for 1,1-dichloroethene; based on results from benchmark dose analysis ($BMCL_{10}$ of 1.59 ppm), adjustment for intermittent exposure, conversion to a human equivalent concentration ($BMCL_{HEC}$) of 0.036 ppm , and an uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability); see Appendix A for more detailed information regarding the MRL.
[c]The intermediate-duration inhalation MRL of 0.001 ppm was adopted as the chronic-duration inhalation MRL; see Appendix A for more detailed information regarding the MRL.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BC = serum (blood) chemistry; Bd wt or BW = body weight; BI = biochemical changes; BM = blood metabolites; Cardio = cardiovascular; CEL = cancer effect level; CS = clinical signs; Develop = developmental; DX = developmental toxicity; EA = enzyme activity; Endocr = endocrine; EX = excretion; F = female(s); FI = food intake; FX = fetal toxicity; GD = gestation day(s); GN = gross necropsy; GSH = glutathione; HE = hematology; Hemato = hematological; HP = histopathology; LC_{50} = lethal concentration, 50% kill; LE = lethality; min = minute(s); LOAEL = lowest-observed-adverse-effect level; M = male(s); mo = month(s); MX = maternal toxicity; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OF = organ function; OW = organ weight; Repro = reproductive; Resp = respiratory; TM = tissue metabolites; UM = urinary metabolites; UR = urinalysis; WI = water intake

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

Acute (≤14 days)

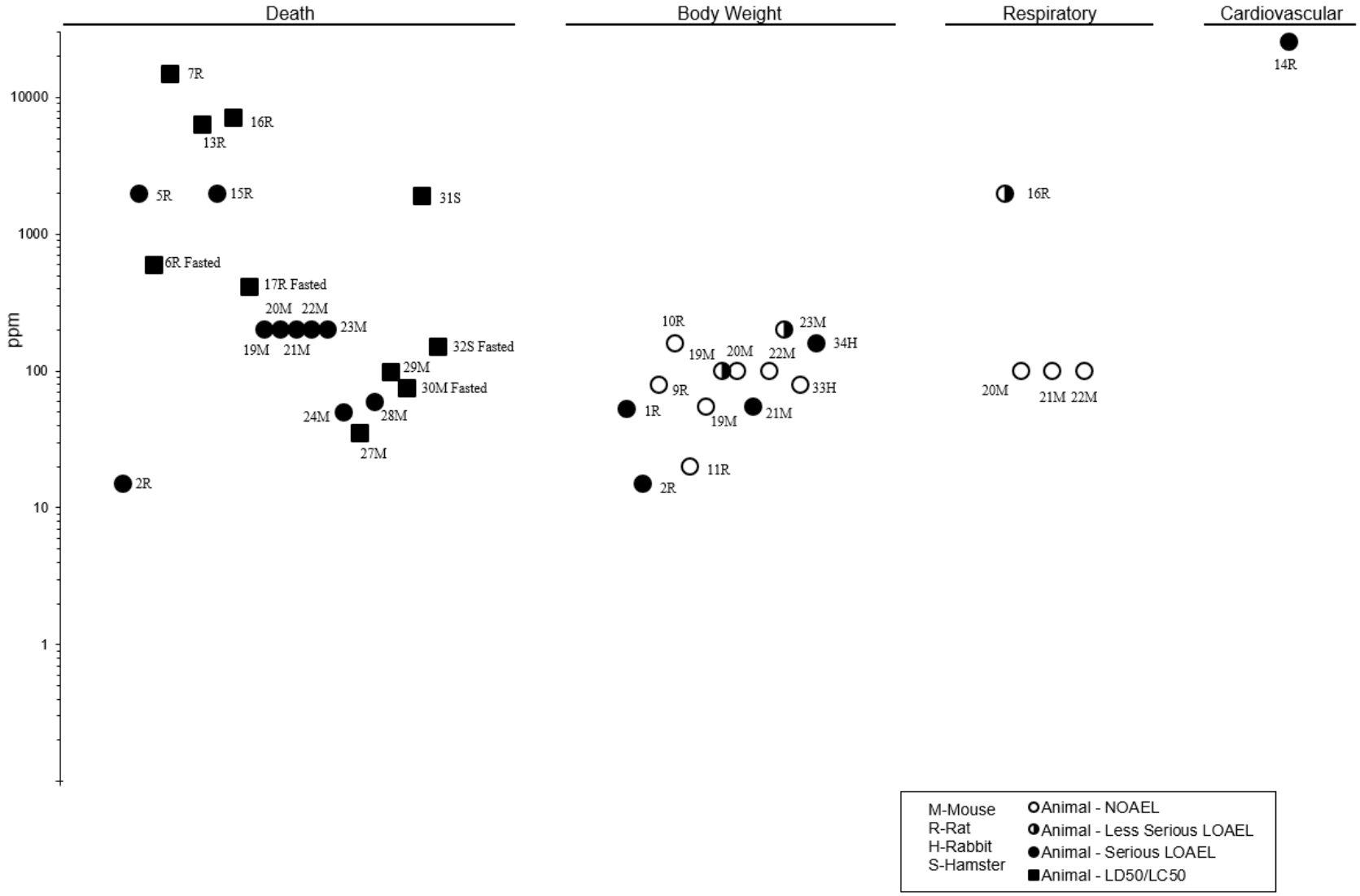


Figure 2-2. Levels of Significant Exposure to 1,1-Dichloroethene – Inhalation

Acute (≤14 days)

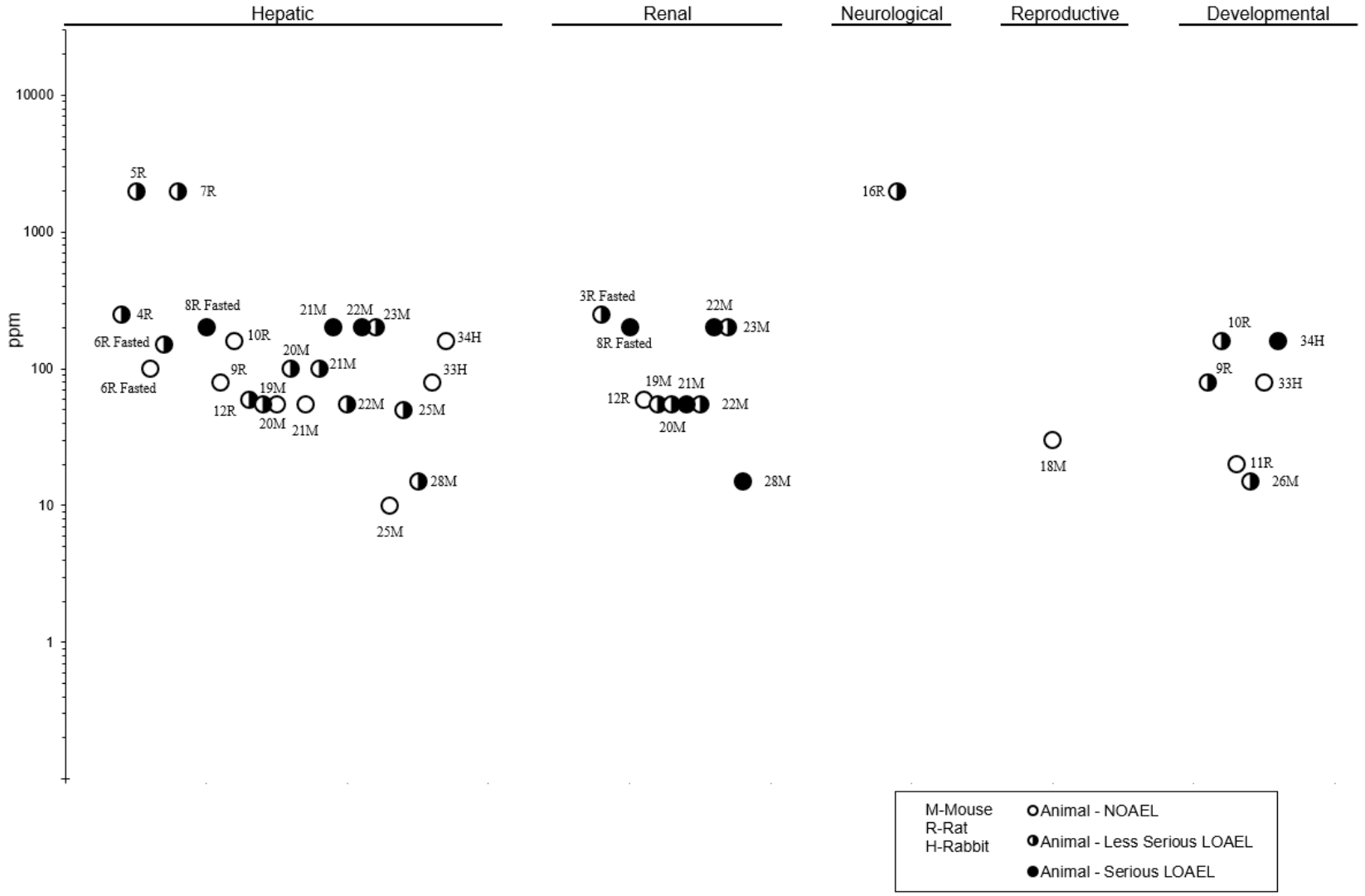


Figure 2-2. Levels of Significant Exposure to 1,1-Dichloroethene – Inhalation

Intermediate (15-364 days)

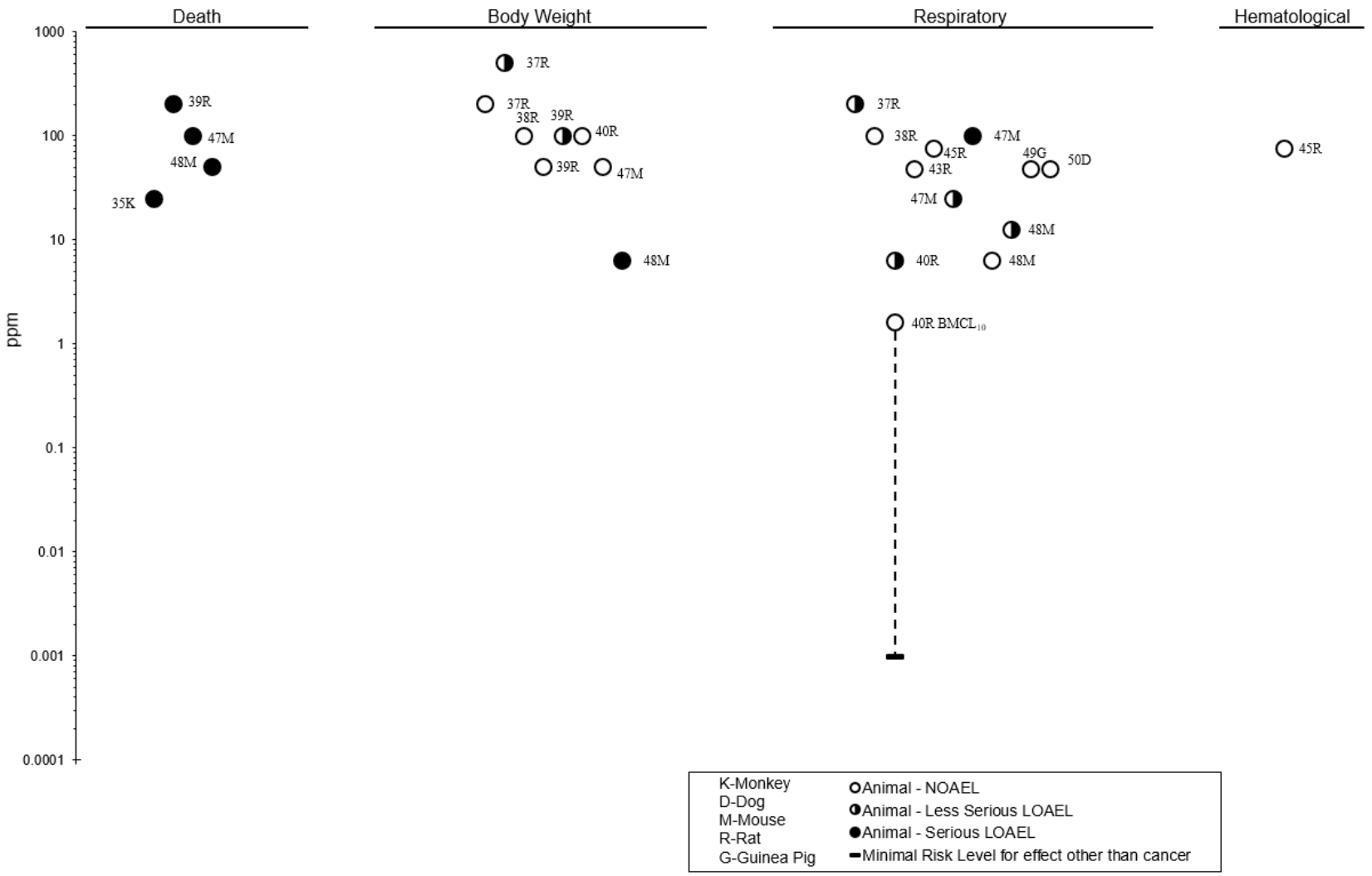


Figure 2-2. Levels of Significant Exposure to 1,1-Dichloroethene – Inhalation

Intermediate (15-364 days)

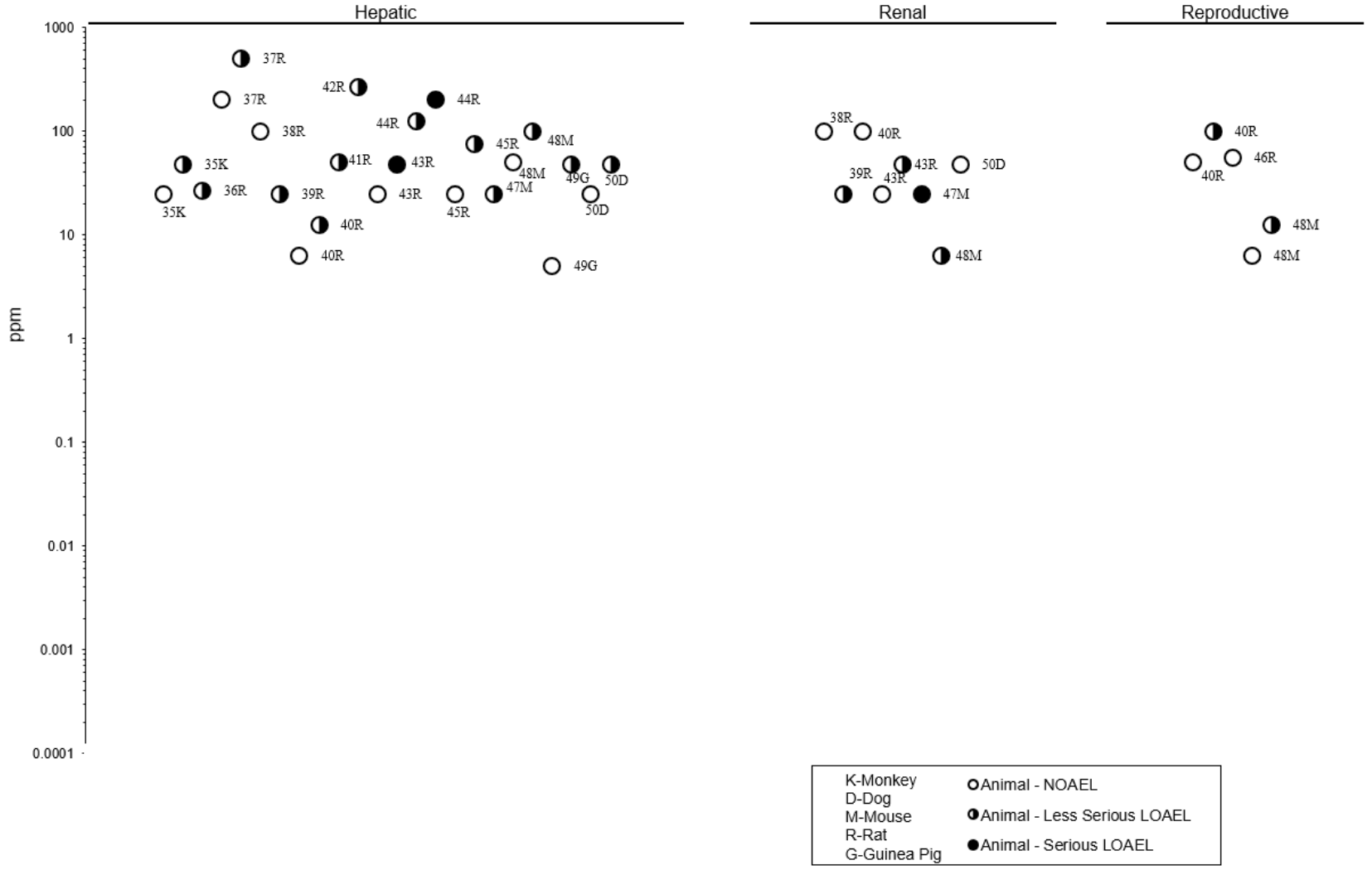


Figure 2-2. Levels of Significant Exposure to 1,1-Dichloroethene – Inhalation

Chronic (≥365 days)

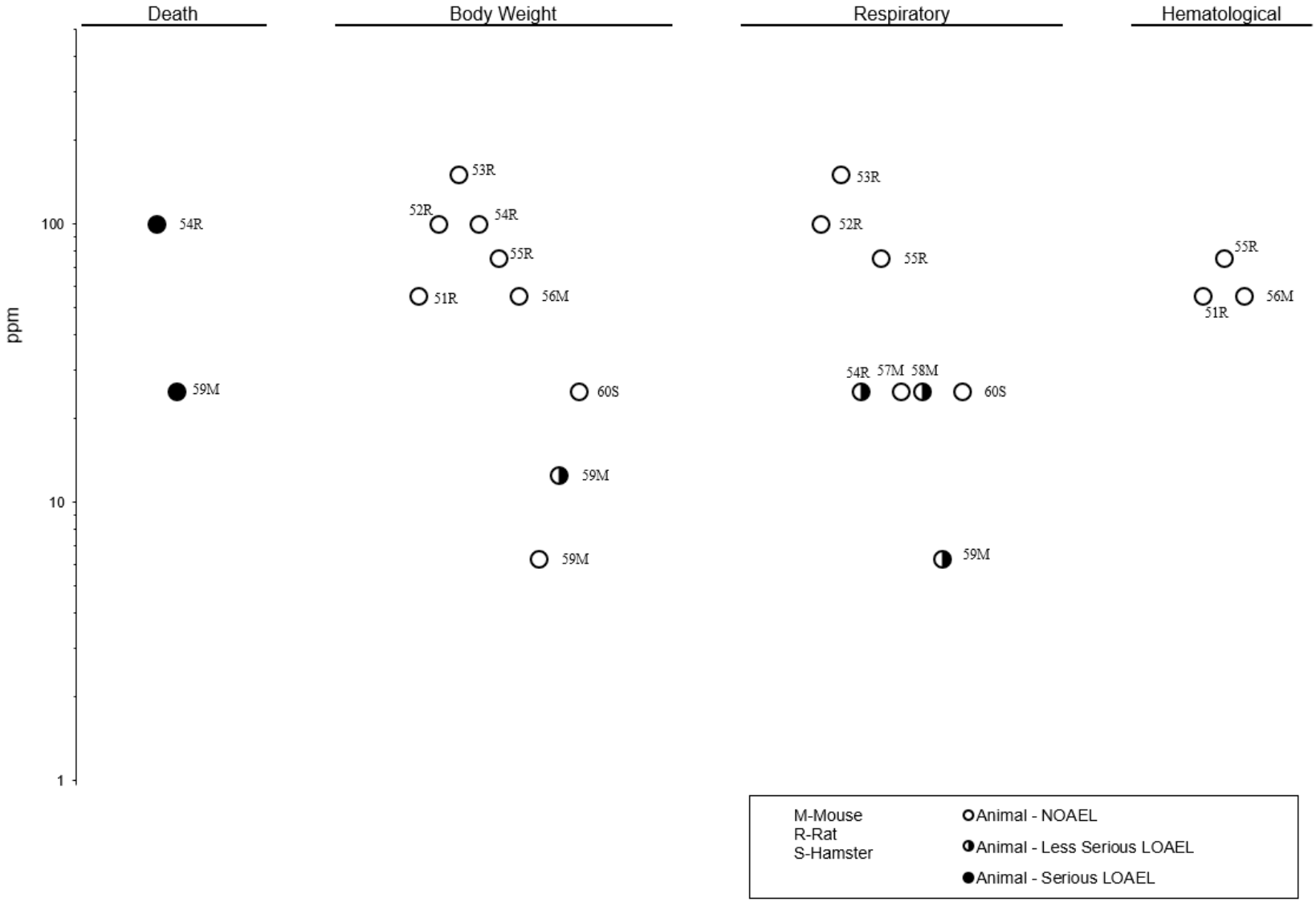


Figure 2-2. Levels of Significant Exposure to 1,1-Dichloroethene – Inhalation

Chronic (≥365 days)

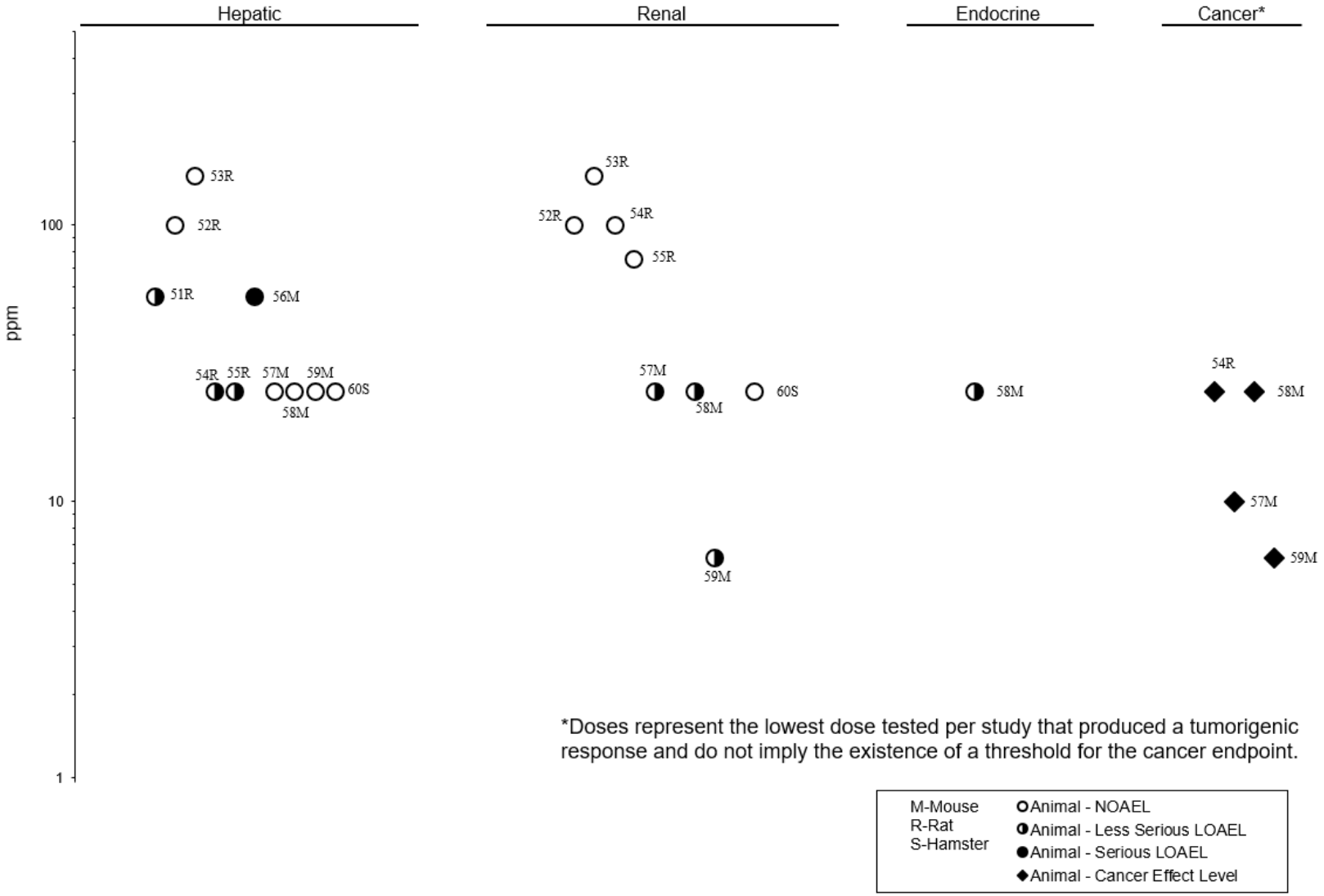


Table 2-2. Levels of Significant Exposure to 1,1-Dichloroethene – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
ACUTE EXPOSURE									
1	Rat (Sprague-Dawley) 3 M (fasted) 4 M (fed)	Once (GO)	0, 200	HP	Resp	200			
					Cardio	200			
					Gastro		200		Edema of forestomach in fasted and nonfasted rats
					Hemato		200		Increased hemoglobin level in fasted rats
					Hepatic			200	Hemorrhagic liver and midzonal necrosis in fasted rats; “minor” liver injury in nonfasted rats
					Renal		200		Granular "heme" casts in Henle's loop in fasted rats; no effect in nonfasted rats
Chieco et al. 1981									
2	Rat (Sprague-Dawley) 3 M	Once (GO)	0, 50, 100, 150, 200	BC, BI	Hepatic		50		Increased ALT and AST activities in fasted rats
Chieco et al. 1981									
3	Rat (Holtzman) 5–37 M	Once (GO)	0, 100, 200, 400, 800	BI, OF	Hepatic		100		Decreased glucose-6-phosphatase and increased serum alanine α-ketoglutarate transaminase activity in fasted rats
Jaeger et al. 1973b									
4	Rat (Sprague-Dawley) 3–6 M	Once (GO)	0, 400	BI, OF	Renal			400	Up to 4.1-fold increased blood urea nitrogen in fasted rats; no effect in nonfasted rats
Jenkins and Andersen 1978									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
5	Rat (Sprague-Dawley) 2–6 M	Once (GO)	0, 50, 100, 200, 400, 600	BC, HP, OW	Renal	200		400	Markedly increased plasma creatinine and urea nitrogen in fasted rats
Jenkins and Andersen 1978									
6	Rat (Sprague-Dawley) 2–7 M, 2–7 F	Once (GO)	400	BI, OF, OW	Renal			400	Markedly increased blood urea nitrogen, increased kidney weight (males only), histopathologic kidney lesions including tubular necrosis and vacuolization in fasted rats
Jenkins and Andersen 1978									
7	Rat (Sprague-Dawley) 2–6 M, 4 F	Once (GO)	400	EA, OF	Hepatic			400	Plasma AST and ALT increased by ≥2-fold in fasted rats
Jenkins and Andersen 1978									
8	Rat (Holtzman) NS	Once (GO)	NS	LE	Death			1,510	96-hour LD_{50} for sham-operated rats in study that included adrenalectomized rats
Jenkins et al. 1972									
9	Rat (Sprague-Dawley) 6–10 M	Once (GO)	0, 25, 50, 100	GN, HP	Hepatic		25		Morphological changes in bile canaliculi and plasma membranes of fasted rats
Kanz and Reynolds 1986									
10	Rat (Sprague-Dawley) 8 M	Once (GO)	0, 100	BI, HP, OF	Hepatic		100		Centrilobular and midzonal necrosis
Kanz et al. 1991									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
11	Rat (Sprague-Dawley) 5–7 M	Once (GO)	0, 200	BI, OF	Hepatic		200		Decreased bile flow, increased plasma levels of AST and LDH in bile-cannulated fasted rats
Moslen et al. 1985									
12	Rat (Sprague-Dawley) 26 F (treated) 24 F (control)	GDs 6–15 *ad libitum* (W)	0, 40	BW, CS, FI, OW, WI	Bd wt Hepatic Develop	40 40 40			
Murray et al. 1979									
13	Rat (F344/N) 5 M, 5 F	14 days 1 time/day (GO)	0, 10, 50, 100, 500, 1,000	BW, CS, GN	Death			1,000 M 500 F	4/5 males died 2/5 females died
					Bd wt	100 M 50 F	100 F	500 M	28% depressed body weight gain in males 11% depressed body weight gain in females
					Hepatic			1,000 M 500 F	Liver necrosis in male and female rats that died
NTP 1982									
14	Rat (BD IV) 4 NS	Once (GO)	NS	LE	Death			1,800 M 1,500 F	LD_{50}
Ponomarkov and Tomatis 1980									
15	Rat (Sprague-Dawley) 5–7 M	Once (GO)	0, 200	BI, HP, OF	Hepatic		200		Cell injury, decreased bile secretion in fasted rats
Reynolds et al. 1984									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
16	Mouse (C57BL/6) 5 or 7 M	Once (GO)	0, 100, 200	HP, OF	Resp		100		Reversible cellular changes in Clara cells (club cells) of bronchiolar epithelium
Forkert and Reynolds 1982									
17	Mouse (C57BL/6) 6 M	Once (GO)	0, 200	BW, HP, OW	Bd wt			200	26% depressed mean body weight at 5 days posttreatment
					Resp		200		Reversible damage and disruption of Clara cells (club cells); increased lung weight
Forkert et al. 1985									
18	Mouse (Alderley Park) 6 M, 6 F	Once (GO)	5 unspecified dose levels	LE	Death			217 M 194 F	LD_{50}
Jones and Hathway 1978a									
19	Mouse (B6C3F1) 5 M, 5 F	Once (GO)	0, 10, 50, 100, 500, 1,000	LE	Death			500	5/5 males died; 3/5 females died
NTP 1982									
20	Mouse (B6C3F1) 5 M, 5 F	14 days 1 time/day (GO)	0, 5, 10, 50, 100, 500	BW, CS, GN	Death			500	100% mortality
					Hepatic			500	Liver necrosis
NTP 1982									
INTERMEDIATE EXPOSURE									
21	Rat (Sprague-Dawley) NS F	61–82 days (premating or premating + gestation) (W)	0, 0.02, 18	BW, CS, FX, HP, MX	Bd wt	18			
Dawson et al. 1993									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
22	Rat (F344/N) 10 M, 10 F	90 days 5 days/week 1 time/day (GO)	0, 5, 15, 40, 100, 250	BW, CS, HP, LE	Death			250	3/10 females died
					Bd wt	100	250		20 and 11% depressed body weight gain in males and females, respectively
					Hepatic	40	100		Hepatocytomegaly in males; fibrosis, pigmentation, bile duct hyperplasia in females; each lesion type increased in males and females at 250 mg/kg/day
NTP 1982									
23	Mouse (B6C3F1) 10 M, 10 F	90 days 5 days/week 1 time/day (GO)	0, 5, 15, 40, 100, 250	BW, CS, HP, LE	Death			100	2/10 males, 3/10 females died at 100 mg/kg/day 10/10 males, 9/10 females died at 250 mg/kg/day
					Hepatic	40	100		Necrosis and other cellular changes at dose level resulting in deaths
NTP 1982									
24	Dog (Beagle) 4 M, 4 F	97 days 1 time/day (capsule)	0, 6.25 12.5, 25	BC, BW, CS, FI, OW	Bd wt	25			
					Hemato	25			
					Hepatic	25			
					Renal	25			
Quast et al. 1983									
CHRONIC EXPOSURE									
25	Rat (Sprague-Dawley) 50 M, 50 F (treated) 75 M, 75 F (control)	52 weeks 4–5 days/week 1 time/day (GO)	0, 0.5	BW, CS, GN, HP, LE	Bd wt	0.5			
					Resp	0.5			
					Hepatic	0.5			
					Renal	0.5			
Maltoni et al. 1985									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
26	Rat (Sprague-Dawley) 50 M, 50 F (treated) 100 M, 100 F (control)	52 weeks 4–5 days/week 1 time/day (GO)	0, 5, 10, 20	BW, CS, GN, HP, LE	Bd wt	20			
					Resp	20			
					Hepatic	20			
					Renal	20			
Maltoni et al. 1985									
27	Rat (F344) 50 M, 50 F	104 weeks 5 days/week 1 time/day (GO)	0, 1, 5	BW, CS, GN, HP	Bd wt	5			
					Resp	5			
					Cardio	5			
					Gastro	5			
					Hepatic	5			
					Renal	5			
NTP 1982									
28	Rat (Sprague-Dawley) 48 M, 48 F (treated) 80 M, 80 F (control)	2 years *ad libitum* (W)	M: 0, 7, 10, 20; F: 0, 9, 14, 30	BC, BW, CS, FI, OW	Hemato	20 M 30 F			
					Hepatic	10 M	20 M 9[b] F		Hepatocellular swelling with midzonal fatty changes in males and females ($BMDL_{10}$ = 4.51 mg/kg/day)
					Renal	20 M 30 F			
Quast et al. 1983									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
29	Mouse (B6C3F1) 50 M, 50 F	104 weeks 5 days/week 1 time/day (GO)	0, 2, 10	BW, CS, GN, HP	Bd wt	10			
					Resp	10			
					Cardio	10			
					Hepatic	10			
					Renal	10			

NTP 1982

[a]The number corresponds to entries in Figure 2-3; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-3. Where such differences exist, only the levels of effect for the most sensitive gender are presented.
[b]Used to derive a chronic-duration oral minimal risk level (MRL) of 0.05 mg/kg/day for 1,1-dichloroethene; based on a $BMDL_{10}$ of 4.51 mg/kg/day for hepatic midzonal fatty change and an uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability); see Appendix A for more detailed information regarding the MRL.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BC = serum (blood) chemistry; Bd wt or BW = body weight; BI = biochemical changes; Cardio = cardiovascular; CS = clinical signs; Develop = developmental; EA = enzyme activity; F = female(s); FI = food intake; FX = fetal toxicity; Gastro = gastrointestinal; GD = gestation day(s); GN = gross necropsy; GO = gavage in oil; Hemato = hematological; HP = histopathology; LD_{50} = lethal dose, 50% kill; LDH = lactate dehydrogenase; LE = lethality; min = minute(s); LOAEL = lowest-observed-adverse-effect level; M = male(s); MX = maternal toxicity; NOAEL = no-observed-adverse-effect level; NS = not specified; OF = organ function; OW = organ weight; Repro = reproductive; Resp = respiratory; W = drinking water; WI = water intake

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

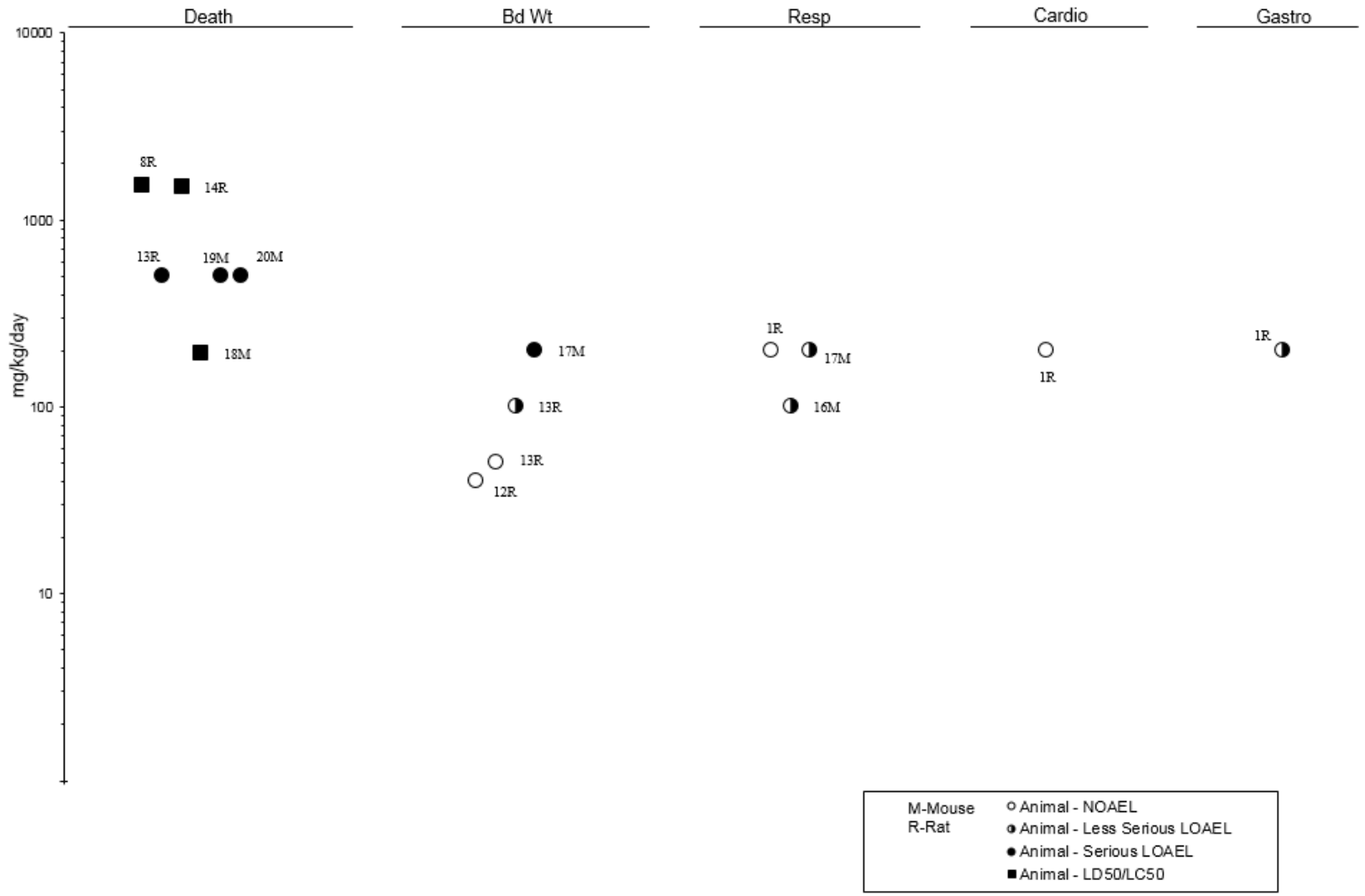


Figure 2-3. Levels of Significant Exposure to 1,1-Dichloroethene – Oral
Acute (≤14 days)

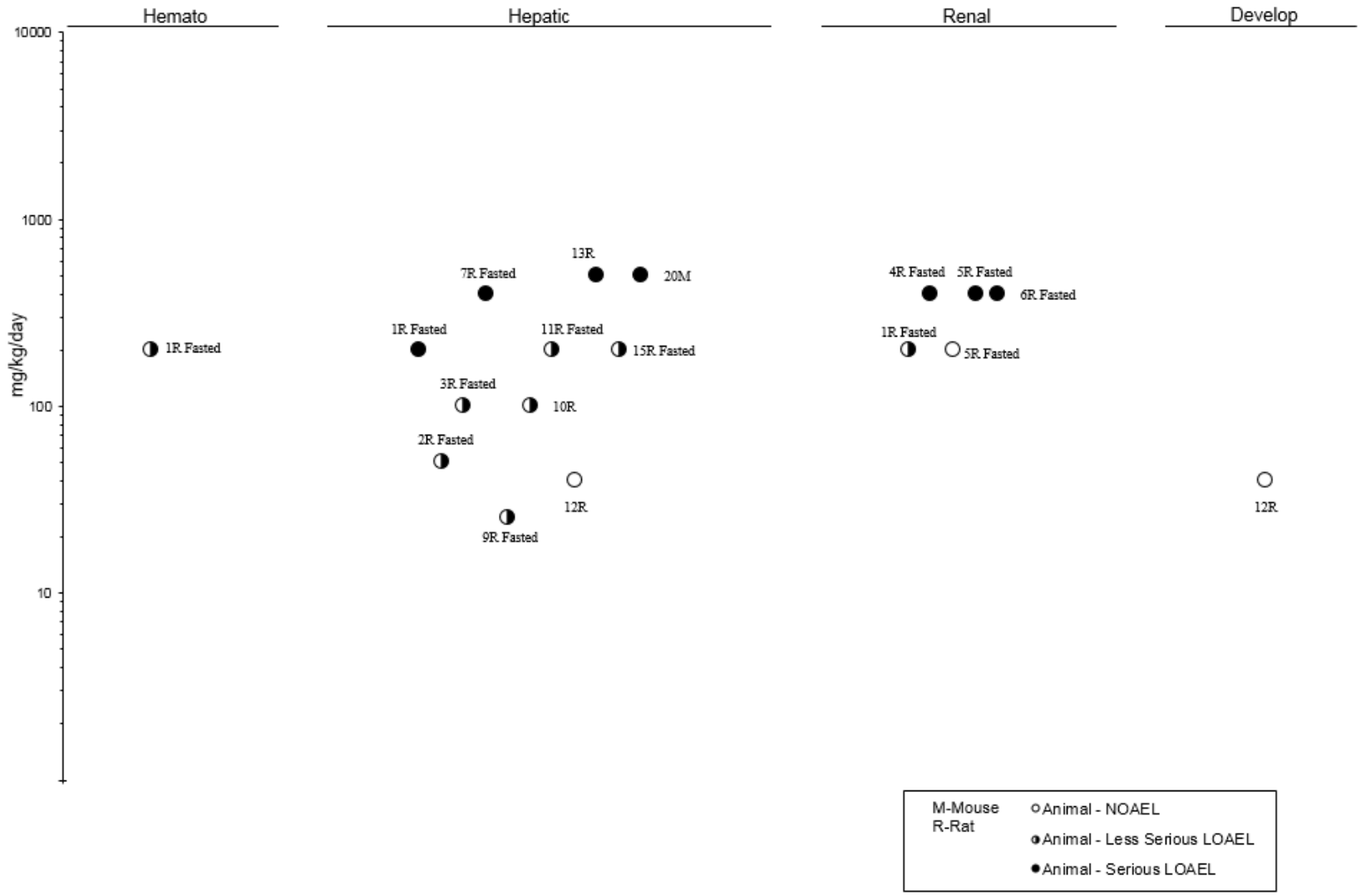


Figure 2-3. Levels of Significant Exposure to 1,1-Dichloroethene – Oral
Intermediate (15-364 days)

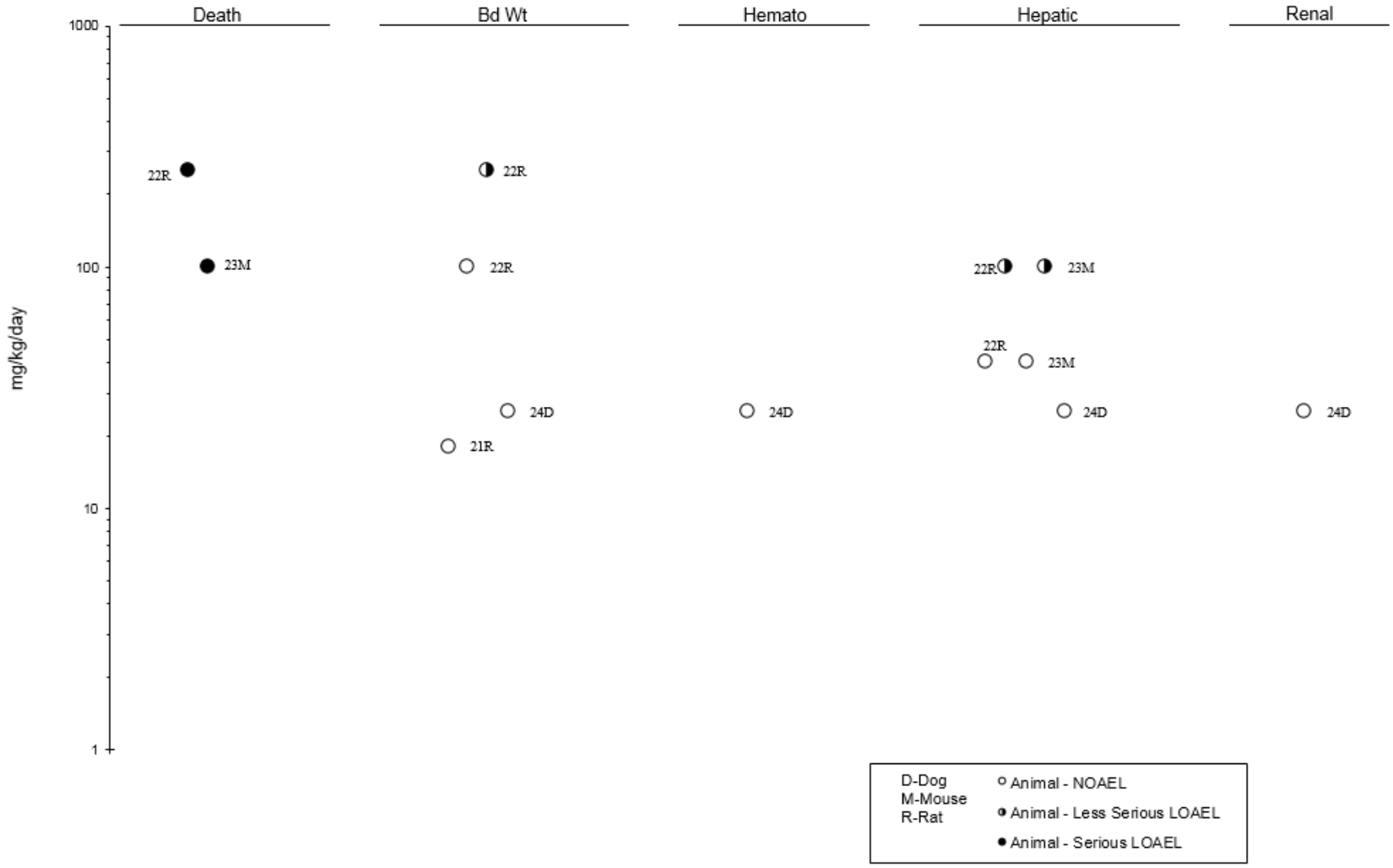
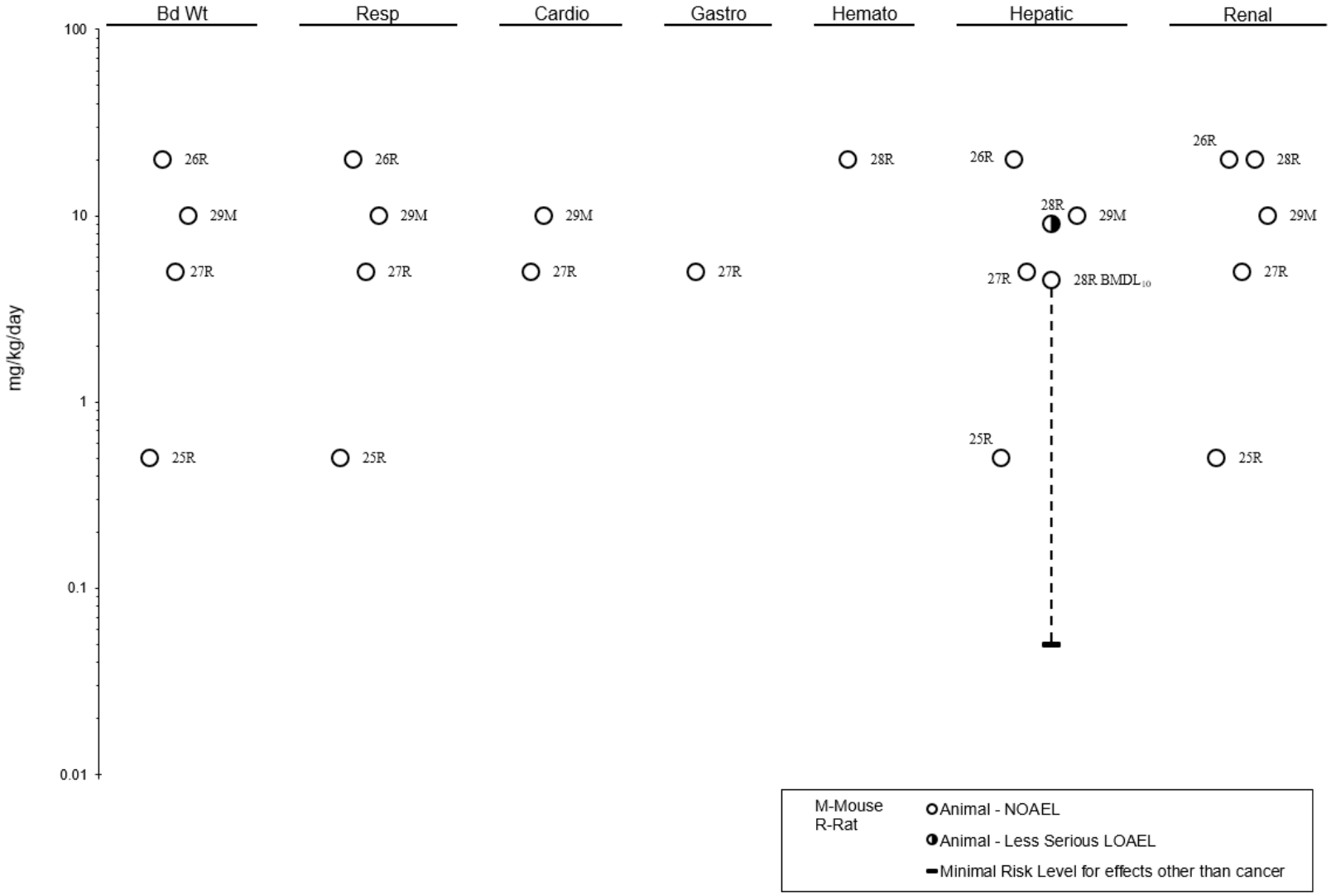


Figure 2-3. Levels of Significant Exposure to 1,1-Dichloroethene – Oral

Chronic (≥365 days)



2.2 DEATH

No studies were located regarding death in humans associated with exposure to 1,1-dichloroethene.

The lethality of 1,1-dichloroethene in animals following inhalation exposure varies considerably and is influenced by such factors as species, strain, sex, and food intake. LC_{50} values for laboratory animals acutely exposed to 1,1-dichloroethene vapor are presented in Table 2-3. Fasted laboratory animals were much more susceptible to the lethal effects of inhaled 1,1-dichloroethene than animals maintained on normal diet, mice were more susceptible than rats, and males were more susceptible than females. Single 4-hour exposure of Sprague-Dawley rats maintained on normal diet resulted in LC_{50} values of 7,145 ppm for males and 10,275 ppm for females (Zeller et al. 1979a); among similarly-exposed Sprague-Dawley rats fasted for 16 hours prior to exposure, 4-hour LC_{50} values were 415 ppm for males and 6,545 ppm for females. Jaeger et al. (1974) reported respective LC_{50} values of 15,000 and 600 ppm for nonfasted and fasted male Holtzman rats exposed to 1,1-dichloroethene vapor for 4 hours. Similar exposures of fed and fasted Chinese hamsters resulted in 4-hour LC_{50} values of 1,915 and 2,945 ppm for fed males and females, respectively, and 150 ppm and 455 ppm for fasted males and females, respectively (Klimisch and Freisberg 1979a, 1979b). Although the effects of fasting on the acute lethality of inhaled 1,1-dichloroethene among fed and fasted mice have not been compared in a single strain, available results indicate that mice are markedly more sensitive than rats. For example, 4-hour LC_{50} values of 98 and 105 ppm were calculated for fed male and female CD-1 mice (Short et al. 1977a, 1977b). Fasting of mice does not appear to significantly affect acute lethality, as indicated by 4-hour LC_{50} values of 75 and 125 ppm for fasted NMRI male and female mice, respectively (Zeller et al. 1979c). The proposed mechanism by which fasting increases the toxicity of 1,1-dichloroethene is discussed in Section 2.21.

Maltoni et al. (1985) evaluated mouse strain and sex differences in 1,1-dichloroethene lethality. Swiss, Balb/c, C3H, and C57Bl strains were exposed to 1,1-dichloroethene vapor for 4 hours/day on 2 consecutive days at 200 ppm. High rates of mortality were noted for male Swiss mice (83.3%), male Balb/c mice (80%), male C57Bl mice (26.7%), and male and female C3H mice (53.3 and 43.3%, respectively). There were no deaths among female Swiss, Balb/c, or C57Bl strains. Henck et al. (1979) exposed several strains (Ha[ICR], B6C3F1, CD-1, CF-W) of mice to 1,1-dichloroethene vapor for 6 hours/day, 5 days/week for 12 days. At 200 ppm, mortality within the first 5 exposure days ranged from 40 to 100% for all strains of male mice and Ha(ICR) and B6C3F1 strains of female mice. Mortality occurred in 1/10 and 0/10 female CF-W and CD-1 mice, respectively.

Table 2-3. Acute Lethality Results Among Laboratory Animals Exposed to 1,1-Dichloroethene Vapor

Exposure scenario	Dietary parameter	Strain	Result	Reference
Rat				
Once 4 hours	Nonfasted	Sprague-Dawley	LC_{50} = 7,145 ppm (M) LC_{50} = 10,275 ppm (F)	Zeller et al. 1979a
			At 2,000 ppm, 6/10 males died	Szabo et al. 1977
		NMRI	LC_{50} = 6,350 ppm (M)	Siegel et al. 1971
		Holtzman	LC_{50} = 15,000 ppm (M)	Jaeger et al. 1974
		Holtzman	At 2,000 ppm, 2/5 males died[a]	Jaeger et al. 1973a
	Fasted	Sprague-Dawley	LC_{50} = 415 ppm (M) LC_{50} = 6,545 ppm (F)	Zeller et al. 1979b
		Holtzman	LC_{50} = 600 ppm (M)	Jaeger et al. 1974
GDs 6–16 23 hours/day	Nonfasted	CD	At 15 ppm, 2/18 maternal rats died	EPA 1977a
Mouse				
Once 4 hours	Fasted	NMRI	LC_{50} = 50 ppm (M) LC_{50} = 125 ppm (F)	Zeller et al. 1979c
Once 23 hours	Nonfasted	CD-1	LC_{50} = 98 ppm (M) LC_{50} = 105 ppm (F)	Short et al. 1977a, 1977b
2 days; 23 hours/day			LC_{50} = 35 ppm (M)	
1–5 days; 23 hours/day			At 60 ppm, 8/10 males died	
3 or 8 days; 6 hours/day		Swiss-Webster	At 50 ppm, up to 68 and 82% mortality in males for 3- and 8-day exposures, respectively[b]	Maltoni et al. 1985
12 days; 5 days/week 6 hours/day		Ha(ICR)	At 200 ppm, 6/10 males and 4/10 females died	Henck et al. 1979
200 ppm exposure level, 4 hours/day for 2 days		Swiss Balb/c C57B1 C3H	Lethality: 83.3% M; 0% F 80% M; 0% F 26.7% M; 0% F 53.3% M; 43.3% F	Maltoni et al. 1985
Hamster				
Once 4 hours	Nonfasted	Chinese	LC_{50} = 1,915 ppm (M) LC_{50} = 2,945 ppm (F)	Klimisch and Freisberg 1979a
	Fasted	Chinese	LC_{50} = 150 ppm (M) LC_{50} = 455 ppm (F)	Klimisch and Freisberg 1979b

[a]Deaths occurred in rats exposed during a period of low glutathione (GSH) activity.
[b]No deaths in female mice similarly exposed for 3 or 8 days.
[c]No deaths in similarly-exposed female Swiss, Balb/c, or C57Bl mice.

F = female(s); GD = gestation day; LC_{50} = lethal concentration, 50% kill; M = male(s)

In a series of acute- and intermediate-duration inhalation studies of rats and mice, high rates of mortality among rats and mice were observed during the first few days at exposure levels as low as 100–200 ppm (NTP 2015a). In chronic-duration studies, decreased survival was observed in rats and mice exposed at the highest exposure levels tested (100 and 25 ppm, respectively) (NTP 2015a).

Reported single-dose oral LD_{50} values were 1,800 and 1,500 mg/kg in male and female rats, respectively (Ponomarkov and Tomatis 1980), and 217 and 194 mg/kg in male and female mice, respectively (Jones and Hathaway 1978a). In repeated-dose studies of rats and mice, high rates of mortality were observed at doses ≥500 mg/kg/day (rats) and ≥250 mg/kg/day (mice) (NTP 1982).

2.3 BODY WEIGHT

Depressed body weight or body weight loss were reported among maternal rats exposed to 1,1-dichloroethene vapor during major portions of gestation at exposure levels as low as 15–56 ppm (EPA 1977a) and rabbits exposed at 160 ppm (Murray et al. 1979). Adverse body weight effects were observed in other repeated-exposure inhalation studies of rats or mice at exposure levels as low as 100–500 ppm (Gage 1970; Henck et al. 1979; NTP 2015a). In a study that employed several strains of mice exposed to 1,1-dichloroethene vapor for 4 hours/day on 2 consecutive days at 200 ppm, depressed body weight (magnitude not specified) was noted for male Swiss and Balb/c strains and male and female C3H and C57Bl strains (Maltoni et al. 1985). A slight decrease in body weight was reported in rabbits exposed to 25 ppm 1,1-dichloroethene continuously for 90 days or to 100 ppm 1,1-dichloroethene intermittently for 6 weeks (Prendergast et al. 1967). In 14-week inhalation studies of B6C3F1/N mice exposed for 6 hours/day, 5 days/week, body weight gain was depressed by 27% in the female mice at the lowest exposure level tested (6.25 ppm) and by 24% in the male mice exposed at 12.5 ppm (NTP 2015a). However, during the first 13 weeks of a similarly-designed 105-week inhalation study (NTP 2015a), the highest exposure level tested (25 ppm) represented a NOAEL for body weight effects and there was no effect on body weight among similarly-exposed male or female mice during the first 13 weeks of a 105-week study. Furthermore, the 105-week study identified overall NOAELs of 6.25 and 12.5 ppm for males and females, respectively. No exposure-related effects were observed in F344/N male or female rats similarly exposed for 14 or 105 weeks at exposure levels as high as 100 ppm (NTP 2015a).

In a series of oral studies of rats and mice repeatedly gavaged with 1,1-dichloroethene, NTP (1982) reported 28% depressed body weight gain in male rats treated for 14 days at 500 mg/kg/day and 11% depressed body weight gain in female rats similarly treated at 100 mg/kg/day. Treatment of rats for

90 days at 250 mg/kg/day resulted in 20 and 11% depressed body weight gain in males and females, respectively. There were no apparent treatment-related adverse body weight effects among similarly treated male and female mice at doses as high as 250 mg/kg/day. Chronic-duration oral studies of rats or mice found no evidence of 1,1-dichloroethene treatment-related effects on body weight (Maltoni et al. 1985; NTP 1982); however, the highest dose levels employed in these studies were considerably lower (0.5–30 mg/kg/day) than the highest doses typically employed in shorter-duration oral studies.

2.4 RESPIRATORY

No studies were located regarding 1,1-dichloroethene exposure-related respiratory effects in humans.

A single 4-hour exposure of Sprague-Dawley rats to 1,1-dichloroethene vapor at 2,000 ppm resulted in panting or gasping (Zeller et al. 1979a). Slight nasal irritation was reported for Alderley Park mice repeatedly exposed for 4 weeks at 200 ppm. Bronchopneumonia was reported in male Swiss mice exposed to 1,1-dichloroethene vapor for 4 hours/day, 4-5 days/week for 52 weeks (Maltoni et al. 1985). No apparent exposure-related respiratory effects were observed in several other studies of rats, mice, dogs, guinea pigs, or hamsters continuously or repeatedly exposed to 1,1-dichloroethene vapor for 15 weeks to 2 years at 25–150 ppm (Maltoni et al. 1985; Prendergast et al. 1967; Quast et al. 1986). However, most studies did not include histopathologic examination of nasal tissues.

The most sensitive exposure-related respiratory effects in rats and mice repeatedly exposed to 1,1-dichloroethene vapor for intermediate or chronic durations included increased lung weight; chronic active inflammation; hyperostosis; nasal turbinate atrophy; and/or olfactory epithelial mineralization, necrosis, atrophy, and/or metaplasia at repeated exposure levels as low as 6.25–25 ppm (NTP 2015a). In intermediate-duration inhalation studies, rats appear to be more sensitive than mice to 1,1-dichloroethene-induced upper respiratory tract lesions (see Table 2-2). Similar comparison of species-specific sensitivity in the chronic studies is not possible because the mice exhibited significantly increased incidences of nasal lesions at the lowest exposure level tested (6.25 ppm), whereas the lowest exposure level tested in the chronic-duration rat study was 25 ppm (NTP 2015a).

Limited information is available regarding 1,1-dichloroethene-induced respiratory effects following oral exposure. No histopathological changes were observed in the lungs of nonfasted or fasted rats administered a single gavage dose of 200 mg/kg (Chieco et al. 1981). Reversible damage and disruption of Clara cells (club cells) and increased lung weight were reported for C57Bl/6 mice administered

1,1-dichloroethene via single gavage at a dose of 200 mg/kg (Forkert et al. 1985). Cellular regeneration was evident within 5 days following treatment.

2.5 CARDIOVASCULAR

No studies were located regarding 1,1-dichloroethene exposure-related cardiovascular effects in humans.

Available animal data are limited. A single 10-minute exposure to 1,1-dichloroethene vapor at 25,600 ppm resulted in cardiac arrhythmias (Siletchnik and Carlson 1974). The study authors noted that the exposure increased the sensitivity of the myocardium to epinephrine, thereby providing a mechanism for the electrocardiographic changes. Cardiac effects, such as contraction of the main vessels, and hyperemia were observed following acute, high-level exposure (500–15,000 ppm) to 1,1-dichloroethene vapor (Klimisch and Freisberg 1979a, 1979b; Zeller et al. 1979b).

Cardiovascular toxicity was not generally observed after more prolonged, lower-level exposure and is, therefore, most likely not a concern for prolonged low-level exposure in humans. There was no evidence of 1,1-dichloroethene treatment-related histological changes in the cardiovascular system of rats administered a single gavage dose of 1,1-dichloroethene at 200 mg/kg (Chieco et al. 1981), rats or mice repeatedly dosed for 104 weeks at up to 5 and 10 mg/kg/day, respectively, (NTP 1982), or other rats or mice repeatedly exposed to 1,1-dichloroethene vapor for 2 years at up to 100 and 25 ppm, respectively (NTP 2015a).

2.6 GASTROINTESTINAL

No studies were located regarding 1,1-dichloroethene exposure-related gastrointestinal effects in humans.

Limited animal data are available. Edema of the forestomach was observed in fasted and nonfasted rats after a single gavage dose of 200 mg/kg (Chieco et al. 1981). However, this alteration was not associated with any discernible degenerative changes, and its relevance to human exposure is unknown. There was no histological evidence of treatment-related gastrointestinal effects among rats or mice repeatedly gavaged with 1,1-dichloroethene for 104 weeks at up to 5 and 10 mg/kg/day, respectively (NTP 1982), or other rats or mice repeatedly exposed to 1,1-dichloroethene vapor for 2 years at up to 100 and 25 ppm, respectively (NTP 2015a).

2.7 HEMATOLOGICAL

Available human data are limited to the evaluation of 138 employees occupationally exposed to 1,1-dichloroethene in processes that did not involve vinyl chloride and matched control workers without exposure to 1,1-dichloroethene (Ott et al. 1976). Exposed subjects were grouped into three exposure categories (<10, 10–24, and >25 ppm) based on 8-hour time-weighted average (TWA) workplace concentrations of 1,1-dichloroethene estimated from job description and air sampling. Duration of employment was used to estimate career exposure. There were no significant differences between 1,1-dichloroethene-exposed subjects and matched controls regarding hematological parameters.

Limited information is available regarding potential 1,1-dichloroethene exposure-related hematological effects. No hematological alterations were observed in Sprague-Dawley rats repeatedly exposed to 1,1-dichloroethene vapor for up to 18 months at 75 ppm (Quast et al. 1986) or CD rats or CD-1 mice exposed for up to 12 months at 55 ppm (Lee et al. 1977, 1978).

A significant increase ($p<0.001$) in plasma free hemoglobin was observed in fasted rats administered a single dose of 200 mg/kg 1,1-dichloroethene in mineral oil or in corn oil (Chieco et al. 1981). The effect was not as marked, although still significant ($p<0.05$), when 1,1-dichloroethene was given to nonfasted rats in either vehicle. According to the investigators, the effect does not represent a true hematological effect, but is due to hemolysis of red cells trapped in the congested sinusoids of the injured liver.

No significant changes in hematological or clinical chemistry parameters were observed in beagle dogs administered encapsulated 1,1-dichloroethene for 97 days at 25 mg/kg/day (Quast et al. 1983). No hematological effects were observed among Sprague-Dawley rats receiving 1,1-dichloroethene from the drinking water for 2 years at 20–30 mg/kg/day (Quast et al. 1983; Rampy et al. 1977).

2.8 MUSCULOSKELETAL

No information was located regarding 1,1-dichloroethene exposure-related musculoskeletal effects in humans or animals.

2.9 HEPATIC

Available human data are limited to the evaluation of 138 employees occupationally exposed to 1,1-dichloroethene in processes that did not involve vinyl chloride and matched control workers without exposure to 1,1-dichloroethene (Ott et al. 1976). Exposed subjects were grouped into three exposure categories (<10, 10–24, and >25 ppm) based on 8-hour TWA workplace concentrations of 1,1-dichloroethene estimated from job description and air sampling. Duration of employment was used to estimate career exposure. There were no significant differences between 1,1-dichloroethene-exposed subjects and matched controls regarding serum liver enzymes.

In laboratory animals, the liver is a major target organ of 1,1-dichloroethene toxicity associated with acute-, intermediate, and chronic-duration inhalation and oral routes of exposure. Hepatotoxicity is evident by the appearance of both biochemical changes such as alterations in serum enzyme levels indicative of liver injury (Chieco et al. 1981; Jaeger 1977; Jaeger et al. 1973a, 1973b, 1974; Jenkins and Andersen 1978; Moslen et al. 1985; Prendergast et al. 1967; Short et al. 1977a, 1977b) and marked histological changes (e.g., midzonal and centrilobular swelling of liver, degeneration, and necrosis of hepatocytes) (Chieco et al. 1981; Gage 1970; Henck et al. 1979; Jaeger et al. 1974; Kanz et al. 1991; Lee et al. 1977, 1978; Maltoni et al. 1985; McKenna et al. 1978a; NTP 1982, 2015a; Plummer et al. 1990; Prendergast et al. 1967; Quast 1976; Short et al. 1977a, 1977b).

Acute-duration inhalation studies have demonstrated that fasted animals are more susceptible than nonfasted animals to 1,1-dichloroethene hepatotoxicity. For example, McKenna et al. (1987a) reported centrilobular degeneration and necrosis in fasted male rats exposed once for 6 hours at 200 ppm, but no signs of hepatic effects in similarly exposed nonfasted male rats. Single 4-hour exposure of fasted male rats to 1,1-dichloroethene vapor at 150 ppm resulted in increased serum alanine α-ketoglutarate transaminase activity, whereas an exposure level of 2,000 ppm was required to cause the same effect in nonfasted male rats (Jaeger et al. 1974). Hemorrhagic livers and midzonal necrosis were observed in fasted male rats administered 1,1-dichloroethene once by gavage at 200 mg/kg; liver injury was described as “minor” in similarly treated nonfasted male rats (Chieco et al. 1981). The influence of food intake prior to exposure suggests that a relationship exists between chemical toxicity and depletion of reduced glutathione (GSH) (Reynolds et al. 1980). GSH is known to be involved in 1,1-dichloroethene metabolism (see Section 3.1.3). GSH levels in rats fed ad libitum exhibited a marked diurnal rhythm; levels were minimal between 7 pm and 1 am and maximal between 7 am and 1 pm (Jaeger et al. 1973a). This increase was prevented in fasted rats, with maximal levels reduced by 50%. Furthermore, the

1,1-dichloroethene-induced hepatotoxicity coincided with the reduction in liver GSH levels (Jaeger et al. 1973a). Nonfasted rats exposed to 1,1-dichloroethene via inhalation during the period of maximal glutathione levels exhibited no signs of hepatotoxicity, but when they were exposed to similar levels of 1,1-dichloroethene during the diurnal period of minimal GSH levels, 40% died and serum enzyme markers increased markedly.

Hepatotoxicity was reported in rats and mice repeatedly exposed to 1,1-dichloroethene vapor. In a series of studies (NTP 2015a), centrilobular cytoplasmic alterations in hepatocytes were observed in rats exposed for 16 days at the lowest exposure level tested (25 ppm). Similar exposure of mice at 25 ppm resulted in 10–14% increased liver weight; centrilobular necrosis was noted at 100 ppm. In 14-week repeated-exposure studies, hepatic cytoplasmic alterations were observed in male and female rats at exposure levels as low as 12.5 and 50 ppm, respectively (NOAELs of 6.25 and 25 ppm, respectively). At 50 and 100 ppm, all male and female rats exhibited hepatic cytoplasmic alterations. Similar exposures of mice resulted in hepatocellular hypertrophy and necrosis in females at 100 ppm (highest exposure level tested; NOAEL of 50 ppm) and a NOAEL of 50 ppm for males (highest exposure level tested). The male rats appeared to be more susceptible than the female rats to 1,1-dichloroethene hepatotoxicity, and the rats appeared to be more susceptible than the mice. In the chronic-duration (104-week) studies, the lowest exposure level tested in rats (25 ppm) resulted in chronic inflammation and diffuse fatty changes in the liver; exposure levels ≥50 ppm resulted in hepatic necrosis and/or cystic degeneration in males and females. There were no signs of exposure-related hepatic effects in mice similarly exposed at up to 25 ppm (the highest exposure level tested). Differences in the ranges of exposure levels (25–100 ppm for rats and 6.25–25 ppm for mice) preclude drawing conclusions regarding the relative susceptibility of the rats and mice to 1,1-dichloroethene hepatotoxicity under the conditions of the chronic studies. 1,1-Dichloroethene exposure-related hepatic effects such as cytoplasmic alterations, fatty changes, and/or focal necrosis were reported in other intermediate- and chronic-duration inhalation studies of laboratory animals exposed at 25–75 ppm (Balmer et al. 1976; Lee et al. 1977, 1978; Plummer et al. 1990; Prendergast et al. 1967; Quast et al. 1986).

1,1-Dichloroethene is particularly hepatotoxic to laboratory animals acutely exposed via the oral route. A complete spectrum of effects indicative of liver toxicity has been observed in animals, and their incidence and severity tend to be dose related. Significant increases in serum enzyme markers of liver damage or dysfunction (alanine aminotransferase and aspartate aminotransferase) have been noted in fasted rats after the ingestion of a single dose of ≥50 mg/kg (Andersen and Jenkins 1977; Jenkins and Andersen 1978; Moslen et al. 1989a). Acute exposure at ≥25 mg/kg induced bile canalicular injury in fasted rats (Kanz

and Reynolds 1986; Moslen et al. 1989b). Histological evidence of liver damage (pyknotic cells) was noted following oral administration of 100 mg/kg to rats (Kanz et al. 1991). Ultrastructural changes in hepatocellular organelles such as morphological changes in bile canaliculi and plasma membranes have also been noted in fasted rats after a single dose of 25 mg/kg (Kanz and Reynolds 1986).

One study was located regarding hepatic effects in animals after intermediate-duration oral exposure to 1,1-dichloroethene. No exposure-related gross or histopathological changes were observed in the livers of beagle dogs given 25 mg/kg/day in drinking water for 97 days (Quast et al. 1983).

Chronic studies have been performed in rats ingesting low levels (9–20 mg/kg/day) of 1,1-dichloroethene for 2 years. After 1 year of treatment, a minimal increase in cytoplasmic vacuolation of hepatocytes was noted (Rampy et al. 1977). After 2 years, a minimal amount of hepatocellular swelling with midzonal fatty change was reported (Quast et al. 1983). Slight hepatocellular changes were observed in rats exposed to 1,1-dichloroethene in the drinking water at levels of 9 mg/kg/day *in utero*, during lactation, and through weaning into adulthood (Nitschke et al. 1983).

2.10 RENAL

No information was located regarding 1,1-dichloroethene exposure-related renal effects in humans.

Adverse effects have been observed in the kidneys of laboratory animals following acute-, intermediate-, and chronic-duration inhalation exposure to 1,1-dichloroethene. These effects are manifested as enzyme changes (decreases in kidney monooxygenase and epoxide hydrolase levels) (Oesch et al. 1983), tubular alterations (hemoglobinuria) (McKenna et al. 1978a), increased kidney weight (Henck et al. 1979; NTP 2015a; Quast et al. 1986), and histological changes (nephropathy; tubular swelling, degeneration, and necrosis; granular casts in renal tubules of males) (Henck et al. 1979; Jackson and Conolly 1985; Lee et al. 1977; McKenna et al. 1978a; NTP 2015a; Prendergast et al. 1967; Reitz et al. 1980; Short et al. 1977a).

Following acute-duration inhalation exposure, the range of concentrations that produced these effects in rats was 50–300 ppm, with the severity of the kidney lesions increasing with increasing concentration and duration of exposure. Male mice are more susceptible than female mice to the acute nephrotoxic effects of inhaled 1,1-dichloroethene and more susceptible than both sexes of rats. Severe histological lesions of the kidney were observed in the male mice following acute-duration inhalation exposure at 10–50 ppm

(Reitz et al. 1980; Short et al. 1977b). Adverse renal effects (characterized by moderate-to-severe nephrosis) were observed in four strains of mice intermittently exposed at 55–200 ppm for 10 days; the effects occurred predominantly in the male mice (Henck et al. 1979). There is evidence that kidney damage in animals after acute-duration inhalation exposure to 1,1-dichloroethene is reversible, although this may depend on the exposure concentration and duration. Tubular regeneration was evident in mice after a single 6-hour exposure at 50 ppm (Reitz et al. 1980).

The amount of food intake appears to be an important determinant of 1,1-dichloroethene-induced nephrotoxicity. Fasted male rats exposed once to 1,1-dichloroethene vapor for 6 hours at 200 ppm exhibited delayed hemoglobinuria and marked tubular degeneration, while similarly exposed nonfasted male rats displayed no treatment-related toxic effects (McKenna et al. 1978a). GSH depletion may play an indirect role in the exacerbation of 1,1-dichloroethene-induced nephrotoxicity in the fasted rat.

NTP (2015a) reported 12–20% decreased mean relative kidney weight in male and female rats repeatedly exposed to 1,1-dichloroethene vapor for 16 days at 25–100 ppm; however, no kidney effects were observed among other rats exposed for up to 104 weeks at exposure levels as high as 100 ppm. Renal effects observed in mice similarly exposed at 25 ppm for 17 days were limited to males and included granular casts and renal tubule necrosis and regeneration. Other exposure-related renal effects in mice included nephropathy in males at concentrations ≥12.5 ppm and 11% increased kidney weight in females at 6.25 ppm in a 14-week study, and increased incidence of renal cysts in males (but not females) at 25 ppm in a 104-week study. These results indicate that male mice are more sensitive than male rats or female rats or mice to 1,1-dichloroethene renal toxicity. Continuous inhalation exposure of rats to 1,1-dichloroethene vapor at 48 ppm for 90 days resulted in nuclear hypertrophy of the renal tubular epithelium (Prendergast et al. 1967). Severe nephrotoxicity occurred in male mice intermittently exposed at 25 ppm for 52 weeks (Maltoni et al. 1985). The reversibility of this effect was not determined. No treatment-related effects were noted in the kidneys of rats intermittently exposed at 25 or 75 ppm for 18 months (Quast et al. 1986). Strain differences may account for the differential susceptibility to 1,1-dichloroethene exposure.

Evidence for 1,1-dichloroethene-induced kidney dysfunction has also been observed in laboratory animals following acute-duration oral exposure. Fasted rats gavaged once with 1,1-dichloroethene at 400 mg/kg exhibited markedly increased plasma urea and creatinine levels; these changes were not observed in similarly treated nonfasted rats (Jenkins and Andersen 1978). In another single-dose study of rats gavaged at 400 mg/kg, histopathological changes (vacuolization, pigmentation, tubular dilation, and

necrosis) were observed. The 1,1-dichloroethene treatment-related renal changes were more severe in females, although some recovery was evident 96 hours after exposure. Histological changes such as granular heme casts in Henle's loop were observed in the kidneys of fasted rats administered a single gavage dose of 1,1-dichloroethene at 200 mg/kg by gavage in either corn oil, mineral oil, or an aqueous solvent (Chieco et al. 1981). As noted for hepatic effects, fasting exacerbates 1,1-dichloroethene-induced nephrotoxicity in animals; no renal effects were observed in nonfasted animals administered single doses of 400 mg/kg (Jenkins and Andersen 1978).

No renal effects were noted in animals following intermediate (Quast et al. 1983) or chronic (Rampy et al. 1977) oral exposure to 1,1-dichloroethene at doses up to 30 mg/kg/day.

2.11 DERMAL

Liquid 1,1-dichloroethene is irritating when applied to the skin of humans (EPA 1979) and animals (Torkelson and Rowe 1981) after exposures lasting only a few minutes. Details concerning these studies are lacking, but it has been suggested that these irritant effects may be due to the inhibitor, p-hydroxy-anisole (monomethyl ether of hydroquinone [MEHQ]), present in these formulations. MEHQ is an antioxidant, which on contact, results in skin depigmentation at concentrations ≥0.25% (Busch 1985).

2.12 OCULAR

1,1-Dichloroethene is an ocular irritant in humans (EPA 1979); this effect has been ascribed to MEHQ. No eye irritation was observed in rats exposed to 1,1-dichloroethene vapor for 18 months at an average concentration of 75 ppm (Quast et al. 1986).

2.13 ENDOCRINE

Available information regarding potential exposure-related endocrine effects is limited. Unspecified adrenal gland changes were reported in Swiss mice exposed to 1,1-dichloroethene vapor at 25 ppm (the only exposure level tested) for 4 hours/day, 4–5 days/week for 52 weeks (Maltoni et al. 1985). Another study showed that male rats administered 1,1-dichloroethene by gavage at 5 mg/kg/day for 2 years exhibited increased incidence of pheochromocytomas, a usually benign tumor in the adrenal gland (NTP 1982).

2.14 IMMUNOLOGICAL

Limited animal data are available regarding 1,1-dichloroethene exposure-related immunological effects. Warbrick et al. (2001) employed the mouse local lymph node assay to evaluate the potential for 1,1-dichloroethene to cause skin sensitivity. Induction with topical applications of 1,1-dichloroethene to the mouse ear followed by injection of [^{3}H]methyl thymidine did not elicit a positive response.

Ban et al. (2003) showed that inhalation exposure of female mice to 1,1-dichloroethene increased the interferon-gamma release in lung-associated lymph nodes, as well as the numbers of IgM producing B cells against sheep red blood cells, indicating that this chemical may promote sensitization through an adjuvant effect—by increasing antigen-presenting activity. In a follow-up study, Ban et al. (2006) tested the adjuvant effect of 1,1-dichloroethene in female mice sensitized to ovalbumin (OVA) without using alum. During the OVA-sensitization period, these mice were repeatedly exposed by inhalation to 1,1-dichloroethene. After two OVA-intratracheal challenges, a mild Th2 immune response was observed in the OVA-exposed groups, a response that was characterized by a mild increase in serum specific IgE level, in local Th2 cytokine production, and in lung inflammatory reaction. Exposure to 1,1-dichloroethene alone markedly increased the Th2 cytokine levels above the levels observed in the groups exposed to OVA alone. A synergistic effect of 1,1-dichloroethene and OVA on cytokine production did not occur; however, 1,1-dichloroethene did potentiate the production of IgE, an influx of inflammatory cells, and goblet cell hyperplasia in the 1,1dichloroethene plus OVA-sensitized mice (Ban et al. 2006).

2.15 NEUROLOGICAL

Central nervous system depression and symptoms of inebriation, which may progress to unconsciousness, have been observed in humans after acute exposure to high airborne concentrations (≈4,000 ppm) of 1,1-dichloroethene (EPA 1979). Complete recovery generally occurs if exposure is not prolonged.

Signs of central nervous system toxicity were observed in animals after acute inhalation exposure. The toxic signs are similar across species and consist primarily of central nervous system depression, dyspnea, and narcosis, ultimately resulting in death (Klimisch and Freisberg 1979a, 1979b; Zeller et al. 1979a, 1979b). These signs can also be accompanied by lethargy, rough coats, and a hunched appearance (Zeller et al. 1979b). Acute exposure of rats to extremely high concentrations (25,600 ppm for 10 minutes) induced increased sympathetic activity, resulting in cardiac arrhythmia (Siletchnik and Carlson 1974).

No adverse neurological effects were identified after oral administration of 1,1-dichloroethene for any exposure duration in animals. The appearance and demeanor of the test animals were not affected in either an intermediate-duration oral study of dogs (25 mg/kg/day for 97 days) or a chronic-duration drinking water study of rats (≤30 mg/kg/day for 2 years) (Quast et al. 1983). However, no sensitive neurological tests were performed.

2.16 REPRODUCTIVE

No information was located regarding 1,1-dichloroethene exposure-related reproductive effects in humans.

The potential reproductive toxicity of 1,1-dichloroethene has been evaluated to some extent in animals. Premating intermittent exposure of male rats to 1,1-dichloroethene vapor at 55 ppm for 11 weeks did not affect their fertility and no pre- or postimplantation losses occurred in untreated pregnant females mated to treated males (Short et al. 1977c). Repeated inhalation exposure of male mice at 10 or 30 ppm for 5 days appeared to have no adverse effect on fertility; however, decreased fertility was observed in male rats exposed at 50 ppm for 5 days (Andersen et al. 1977). The study authors attributed the decrease to infertility in males that were included in the study to establish a sufficient group size. However, this could not be confirmed due to a lack of sufficient study details. In 14-week inhalation studies (NTP 2015a), 5% decreased sperm motility and 15–16% decreased spermatid count were observed in male F344/N rats intermittently exposed at 100 ppm; 19% decreased epididymal sperm count was noted in male B6C3F1/N male mice intermittently exposed at 12.5 ppm. There was no treatment-related effect on reproduction or neonatal development in a 3-generation study of rats administered 1,1-dichloroethene in the drinking water of rats at concentrations resulting in doses as high as 30 mg/kg/day (Nitschke et al. 1983).

2.17 DEVELOPMENTAL

Available human data are restricted to population-based, cross-sectional studies conducted in northern New Jersey for the years 1985–1988 (Bove et al. 1995). Odds ratios (ORs) were reported for exposure to total dichloroethylenes at levels >2 µg/L in public drinking water and selected developmental endpoints; ORs were 1.71 (99% confidence limit [CL] 0.40, 6.31) for oral cleft defects (based on six cases), 2.52 (99% CL 0.84, 7.56) for central nervous system defects (based on six cases), and 2.60 (99% CL

0.60, 9.76) for neural tube defects (based on four cases). However, the drinking water contained multiple other contaminants, including chlorinated disinfection byproducts.

The potential for 1,1-dichloroethene exposure-related developmental effects has been assessed to some extent in animals (Dawson et al. 1993; Murray et al. 1979; EPA 1977a).

In a series of studies that employed gestational exposure of laboratory animals to 1,1-dichloroethene vapor for up to 23 hours/day (EPA 1977a, Short et al. 1977c), most developmental effects (skeletal anomalies, soft tissue anomalies, decreased pup weight, fetal resorptions) occurred at exposure levels that induced maternal toxicity (e.g., decreased maternal body weight, death). However, increased incidences of unossified incus and incompletely ossified sternebrae were observed in fetuses from maternal mice exposed to 1,1-dichloroethene vapor at 15 ppm (an exposure level not resulting in maternal toxicity) for up to 23 hours/day (EPA 1977a). No evidence of exposure-related developmental neurotoxicity was observed among surviving pups subjected to a battery of behavioral tasks when tested at various lactational days (postnatal days 1–21) following gestational exposure via their mothers exposed to 1,1-dichloroethene vapor at concentrations as high as 283 ppm during gestation (Short 1977a).

Significantly increased incidences of wavy ribs and delayed ossification of skull and/or cervical vertebrae were noted in litters from maternal rats exposed to 1,1-dichloroethene vapor during gestation at 80 or 160 ppm; complete fetal resorptions were observed among maternal rabbits similarly exposed at 160 ppm (the only exposure level tested) (Murray et al. 1979). However, significantly decreased maternal body weight gain was also noted at these exposure concentrations. There is some degree of uncertainty regarding the role of maternal body weight gain in the observed developmental effects.

There was no indication of exposure-related effects on the number of implantations, live fetuses, resorptions, sex ratio, fetal weight, or incidence of malformations among the offspring of rats receiving 1,1-dichloroethene from the drinking water during gestation at an estimated dose of 40 mg/kg/day (Murray et al. 1979). A marginal increase in crown-rump length was noted; the significance of this result is unclear.

Among groups of timed-mated rats receiving 1,1-dichloroethene from the drinking water at estimated doses of 0, 0.02, or 18 mg/kg/day for periods prior to mating or prior to mating and during gestation, there were no signs of maternal toxicity and no evidence of significant effects on percentage of live births, implantations, or resorptions, or incidences of congenital abnormalities other than cardiac (Dawson et al.

1993). The study authors reported significantly increased incidence in the percentage of fetuses with cardiac changes following maternal exposure during both premating and gestation periods (7/232 fetuses [3%] for controls; 14/121 [12%] for the low-dose group; 24/184 [13%] for the high-dose group). In additional data provided to EPA (IRIS 2002), numbers of affected litters among controls and low- and high-dose groups were 5/21 (24%), 8/11 (73%), and 13/17 (76%), respectively. The mean numbers of affected fetuses per litter for affected litters only were 1.40, 1.75, and 1.85, respectively. The mean numbers of affected fetuses per litter for all litters were 0.33, 1.27, and 1.41, respectively. EPA (IRIS 2002) noted a lack of dose-response relationship for cardiac malformations, a lack of biologically significant effects on growth or survival in a 3-generation study of Sprague-Dawley rats (Nitschke et al. 1983), and no report of cardiac effects in a prenatal developmental toxicity study (Murray et al. 1979), although this study did not include exposure throughout the entire gestational period. EPA (IRIS 2002) noted that the exposure levels employed by Dawson et al. (1993) were below the level of saturation in the rat liver, and that 1,1-dichloroethene would have been metabolized in the maternal liver and would have reacted with GSH or macromolecules in the liver such that parent compound and/or reactive metabolites would not have likely reached the fetus in significant amounts. These arguments suggest that the reported cardiac changes were of questionable biological significance.

2.18 OTHER NONCANCER

No studies were located regarding other noncancer effects in humans or animals exposed to 1,1-dichloroethene.

2.19 CANCER

Only two studies were available for analysis of possible associations between exposure to 1,1-dichloroethene and risk of cancer in humans. Chronic occupational exposure to 1,1-dichloroethene was not associated with the occurrence of angiosarcoma in rubber-plant workers (Waxweiler 1981). Similarly, no association was found between occupational exposure and cancer mortality in 1,1-dichloroethene production and polymerization plant workers (Ott et al. 1976). The Ott et al. (1976) study is limited in its usefulness in assessing the cancer risk to humans exposed to 1,1-dichloroethene. The cohort size was limited, the observation period was too short, and there was a small number of deaths from specific causes. No allowance was made for a latency period; thus, potential risk was underestimated.

The carcinogenicity of inhaled 1,1-dichloroethene in laboratory animals has been evaluated in several studies and multiple species (Hong et al. 1981; Lee et al. 1977, 1978; Maltoni et al. 1982, 1985; NTP 2015a; Quast et al. 1986; Rampy et al. 1977; Viola and Caputo 1977).

Significantly increased incidences of malignant mesothelioma (all organs) were observed in male rats exposed to 1,1-dichloroethene vapor for up to 104 weeks at 25, 50, and 100 ppm (12/50, 28/50, and 23/50, respectively, versus 1/50 for controls) (NTP 2015a). Significantly increased incidences of the following tumor types were observed in female rats: C-cell adenoma at 100 ppm (11/50 versus 3/50 for controls), C-cell adenoma or carcinoma (combined) at 25 and 100 ppm (incidences among 0, 25, 50, and 100 ppm groups were 3/50, 10/50, 8/48, and 13/50, respectively), and mononuclear cell leukemia at 100 ppm (25/50 versus 10/50 for controls). Marginally significantly increased incidence of nasal respiratory epithelium adenoma was noted in males at 100 ppm (4/50 versus 0/49 controls; p=0.051). Male mice, similarly exposed at 6.25, 12.5, or 25 ppm, exhibited significantly increased incidences of renal tubule adenoma (5/50, 19/50, and 10/50, respectively), versus 0/50 controls, carcinoma (7/50, 31/50, and 18/50, respectively, versus 0/50 controls), and adenoma or carcinoma combined (11/50, 37/50, and 27/50, respectively, versus 0/50 controls). Female mice exhibited significantly increased incidences of alveolar/bronchiolar carcinoma at 12.5 ppm (7/50 versus 1/50 controls; exceeded the incidence for historical controls) but not at 25 ppm (5/49 versus 1/50 controls), hepatocellular carcinoma at 25 ppm (17/50 versus 8/50 controls) and adenoma or carcinoma combined at 12.5 and 25 ppm (37/50 and 38/50, respectively, versus 28/50 controls), hemangiosarcoma in the liver at 25 ppm (6/50 versus 1/50 controls), and hemangioma or hemangiosarcoma (combined) in all organs (combined) (11/50 versus 4/50 controls) at 25 ppm.

Significantly increased incidences of the following tumor types were noted in Swiss mice repeatedly exposed to 1,1-dichloroethene vapor for 52 weeks at 25 ppm and observed until spontaneous death: kidney adenocarcinoma in males (20.8 versus 0% of controls), pulmonary tumors (predominantly adenomas, a few cases of adenocarcinoma) in males and females (13.3 and 9.2%, respectively, versus 3.4% among control males and females), mammary gland adenocarcinomas in females (12/120 versus 1/90 controls), and any tumor (37.5 and 34.4% for males and females, respectively, versus 10.3 and 15.7% among respective controls) (Maltoni et al. 1985). Renal adenocarcinomas are rare tumors in the Swiss mouse. The kidney tumors were accompanied by severe nephrotoxic effects including nephrosis.

Increased incidences of mammary tumors (fibroma, fibroadenoma, adenocarcinoma, sarcoma, carcinosarcoma) and leukemia were reported in rats intermittently exposed to 1,1-dichloroethene vapor at

100 ppm for 104 weeks (Cotti et al. 1988; Maltoni et al. 1985). Pregnant female rats were exposed on GD 12; the exposures continued in dams and ≈50% of the offspring (in ≥12-day-old embryos via transplacental exposure, followed by inhalation exposure for all progeny from this group) for 104 weeks. The remaining ≈50% were exposed for 15 weeks only. The highest tumorigenic response was seen in offspring treated for 104 weeks. The study authors concluded that under these conditions (high exposure concentrations during and after embryonal development), 1,1-dichloroethene is carcinogenic in rats.

Results of other inhalation studies with laboratory animals were negative regarding carcinogenicity (Hong et al. 1981; Lee et al. 1977, 1978; Maltoni et al. 1982, 1985; Quast et al. 1986; Rampy et al. 1977; Viola and Caputo 1977). The negative findings of various inhalation studies may be partially explained by inadequate test conditions. Chronic-duration animal studies at or near the maximum tolerated dose are necessary to ensure an adequate power for the detection of carcinogenic activity (EPA 1986a). Study limitations for many of these investigations included less-than-lifetime exposure, use of concentrations well below or above the maximum tolerated dose (MTD), small numbers of animals, and/or limited gross or microscopic examinations. These limitations impair the sensitivity of a test to detect a carcinogenic response. It should be noted that exposures at or above a particular MTD may be orders of magnitude higher than levels relevant to likely human exposure scenarios.

Several chronic studies in rats and mice evaluated the potential carcinogenicity of 1,1-dichloroethene administered by the oral route (Maltoni et al. 1982, 1985; NTP 1982; Ponomarkov and Tomatis 1980; Quast et al. 1983; Rampy et al. 1977). Dosages of 1,1-dichloroethene in these studies ranged from 0.5 to 150 mg/kg/day. Administration was by gavage (Maltoni et al. 1982, 1985; NTP 1982; Ponomarkov and Tomatis 1980) or via the drinking water (Quast et al. 1983; Rampy et al. 1977). Trends toward increased incidences of tumors were reported in some animal studies (NTP 1982; Ponomarkov and Tomatis 1980; Quast et al. 1983). For example, rats, exposed *in utero* to a single dose of 1,1-dichloroethene at 150 mg/kg followed by weekly gavage doses at 50 mg/kg from weanling until 120 weeks of age, exhibited increased incidences of meningiomas and liver cell adenomas and carcinomas compared to controls, but statistical significance was not achieved in pairwise comparisons (Ponomarkov and Tomatis 1980). However, hyperplastic nodules of the liver in these animals were significantly increased. Another study showed that male rats administered 1,1-dichloroethene by gavage at 5 mg/kg/day for 2 years exhibited nonstatistically significant increased incidence of pheochromocytomas (NTP 1982). Statistically significant increased incidences of combined mammary gland fibroadenomas and adenofibromas were noted in female rats receiving 1,1-dichloroethene from the drinking water for up to 2 years at an estimated dose of 9 mg/kg/day (Quast et al. 1983; some data also reported in Rampy et al. 1977; more detailed

study results reported in Humiston et al. 1978). Because the incidences of these types of tumors were within the normal range of historical control data and these tumor types were not observed in females at higher doses or any group of treated males, the study authors did not consider these increases to be related to 1,1-dichloroethene ingestion. No biologically significant neoplastic effects were observed in rats repeatedly administered 1,1-dichloroethene by gavage for 52 weeks at up to 20 mg/kg/day and observed until natural death (Maltoni et al. 1985). It should be noted that exposures at or above the MTD may be orders of magnitude higher than levels relevant to likely human exposure scenarios.

Clinical signs of toxicity were not generally observed in the various oral carcinogenicity studies on 1,1-dichloroethene; consequently, the MTDs may not have been achieved (NTP 1982; Ponomarkov and Tomatis 1980; Quast et al. 1983; Rampy et al. 1977). Two of the oral carcinogenicity studies also used exposure periods that were less than lifetime (52–59 weeks); however, the animals were observed for 136 or 147 weeks, allowing an adequate latency period for the development of late-appearing tumors (Maltoni et al. 1982, 1985).

The carcinogenicity of 1,1-dichloroethene following dermal exposure was evaluated in Swiss mice (Van Duuren et al. 1979). No skin tumors were noted in animals following repeated dermal applications for up to 588 days at doses of 40 or 121 mg (1,333 or 4,033 mg/kg, respectively). Increased incidences of pulmonary papillomas and squamous-cell carcinomas of the forestomach were observed in similarly treated mice; the incidences of these tumors, however, were not statistically different from controls. The results suggest that 1,1-dichloroethene is inactive as a complete carcinogen (an agent that, if applied in sufficient concentrations, can induce tumors by itself) when applied repeatedly to the mouse skin. However, in a tumor initiation/promotion portion of the study using 1,1-dichloroethene in the initiation portion followed by repeated dermal application of the tumor promotor, phorbol myristate acetate, there was a statistically significant increase in the incidence of skin papillomas compared to controls. These results indicate that 1,1-dichloroethene may function as a tumor-initiating agent.

The Department of Health and Human Services (HHS) has not evaluated the carcinogenicity of 1,1-dichloroethene (NTP 2016). EPA (IRIS 2002) reviewed available human and animal data and concluded that 1,1-dichloroethene “exhibits *suggestive evidence* of carcinogenicity but not sufficient evidence to assess human carcinogenic potential following inhalation exposure in studies of rodents.” EPA (IRIS 2002) also noted “the data for 1,1-dichloroethene are *inadequate* for an assessment of human carcinogenic potential by the oral route.” IARC recently assigned 1,1-dichloroethene to Group 2B, based

on “sufficient evidence of carcinogenicity in laboratory animals” and no data or “inadequate evidence” in humans (Grosse et al. 2017).

2.20 GENOTOXICITY

The available data suggest that 1,1-dichloroethene produced genotoxic effects in a variety of test systems. In many of the assays, metabolic activation was required. Results from *in vitro* genotoxicity studies are shown in Table 2-4. Gene mutations were observed in most assays using bacteria, yeast, or plant cells (Baden et al. 1977; Bartsch et al. 1979; Bronzetti et al. 1981; Greim et al. 1975; Jones and Hathway 1978b; Malaveille et al. 1977; Oesch et al. 1983; Roldan-Arjona et al. 1991; Strobel and Grummt 1987; Van’t Hof and Schairer 1982; Waskell 1978). 1,1-Dichloroethene induced gene conversion in yeast (Bronzetti et al. 1981; Koch et al. 1988). Dose-dependent increases in the frequency of euploid whole chromosome segregants were noted in *Aspergillus nidulans* (Crebelli et al. 1992). Both base-pair substitution and frameshift mutations were reported in *Salmonella typhimurium* after continuous exposure to 1,1-dichloroethene vapor (Bartsch et al. 1979; Jones and Hathway 1978b; Oesch et al. 1983). Negative results for gene mutation were obtained in a few assays that employed liquid exposure of selected *Salmonella typhimurium* strains (Mortelmans et al. 1986; NTP 2015a; Strobel and Grummt 1987). Given that 1,1-dichloroethene is very volatile and would be expected to escape from the culture, continuous exposure to vapor is considered a more reliable method to employ for testing the genotoxicity of 1,1-dichloroethene in *in vitro* assays. 1,1-Dichloroethene was mutagenic in *S. typhimurium* following metabolic activation with an exogenous activation system derived from human liver cells (Jones and Hathway 1978b), thus providing some evidence that mutagenic metabolites of 1,1-dichloroethene could be formed in the human liver.

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

Species (test system)	Endpoint	Results		Reference
		With activation	Without activation	
Prokaryotic organisms:				
Salmonella typhimurium TA100, TA1535 (gas exposure)	Gene mutation	+	–	Baden et al. 1977
S. typhimurium TA100 (gas exposure)	Gene mutation	+	No data	Bartsch et al. 1979
S. typhimurium TA92, TA98, TA100, TA135, TA137 (gas exposure)	Gene mutation	+	–	Oesch et al. 1983

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

Species (test system)	Endpoint	Results		Reference
		With activation	Without activation	
S. typhimurium TA1535 (gas exposure)	Gene mutation	+	No data	Jones and Hathway 1978b
S. typhimurium TA100 (gas exposure)	Gene mutation	+	No data	Malaveille et al. 1977
S. typhimurium TA98, TA100 (gas exposure)	Gene mutation	+	+	Waskell 1978
S. typhimurium TA98, TA100, TA1535, TA1538 (liquid exposure)	Gene mutation	–	–	Mortelmans et al. 1986
S. typhimurium TA98, TA100, TA1535, TA1537 (liquid exposure)	Gene mutation	–	–	NTP 2015a
S. typhimurium BA13/BAL13 (liquid exposure)	Gene mutation	+	–	Roldan-Arjona et al. 1991
S. typhimurium TA97 (liquid exposure)	Gene mutation	+	–	Strobel and Grummt 1987
S. typhimurium TA98 (liquid exposure)	Gene mutation	–	–	Strobel and Grummt 1987
S. typhimurium TA100 (liquid exposure)	Gene mutation	+	+	Strobel and Grummt 1987
S. typhimurium TA104 (liquid exposure)	Gene mutation	(+)	+	Strobel and Grummt 1987
Escherichia coli WP2 *uvrA* (gas exposure)	Gene mutation	+	–	Oesch et al. 1983
E. coli K12 (liquid exposure)	Gene mutation	+	–	Greim et al. 1975
Eukaryotic organisms:				
Fungi:				
Saccharomyces cerevisiae D7 (liquid exposure)	Gene mutation	+	–	Bronzetti et al. 1981
S. cerevisiae D7(liquid exposure)	Gene mutation	+	–	Koch et al. 1988
S. cerevisiae D7 (liquid exposure)	Gene conversion	+	–	Bronzetti et al. 1981
S. cerevisiae D7 (liquid exposure)	Gene conversion	–	–	Koch et al. 1988
S. cerevisiae D61.M (liquid exposure)	Mitotic malsegregation	+	+	Koch et al. 1988
Aspergillus nidulans (liquid exposure)	Chromosome malsegregation	+	No data	Crebelli et al. 1992
Plant:				
Tradescantia clone 4430 (gas exposure)	Gene mutation	No data	(+)	Van't Hoff and Schairer 1982

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

Species (test system)	Endpoint	Results		Reference
		With activation	Without activation	
Mammalian cells:				
Chinese hamster V79 cells (gas exposure)	Gene mutation	–	No data	Drevon and Kuroki 1979
Mouse L5178Y lymphoma cells (gas exposure)	Gene mutation	+	(+)	McGregor et al. 1991
Mouse L5178Y lymphoma cells (gas exposure)	Gene mutation	+	+/–	NTP 2015a
Chinese hamster DON-6 cells (liquid exposure)	Chromosomal breakage	–	No data	Sasaki et al. 1980
Chinese hamster lung cells (liquid exposure)	Chromosomal aberrations	+	–	Sawada et al. 1987
Chinese hamster lung cells (liquid exposure)	Sister chromatid exchange	(+)	–	Sawada et al. 1987

+ = positive result; (+) = weakly positive result; +/– equivocal result; – = negative result

1,1-Dichloroethene was negative in a point mutation assay that employed cultured 8-azaguanine and ouabain-resistant V79 Chinese hamster lung cells (Drevon and Kuroki 1979), but it produced chromosomal aberrations and sister chromatid exchanges in a Chinese hamster lung fibroblast cell line (Sawada et al. 1987). 1,1-Dichloroethene induced gene mutations in mouse lymphoma cells (McGregor et al. 1991; NTP 2015a) in the presence of a metabolic activation system; weakly positive or equivocal results were obtained in the absence of exogenous metabolic activation (McGregor et al. 1991; NTP 2015a).

1,1-Dichloroethene has also been tested in several *in vivo* studies in animals; results are summarized in Table 2-5. In general, 1,1-dichloroethene did not demonstrate genotoxicity in mammalian studies *in vivo*. 1,1-Dichloroethene did not induce sex-linked recessive lethal mutations in germ cells of male *Drosophila melanogaster* exposed by feeding or injection (Foureman et al. 1994; also reported in NTP 2015a). 1,1-Dichloroethene did not induce chromosomal aberrations in rats intermittently exposed by inhalation at up to 75 ppm for up to 2 years (Rampy et al. 1977). 1,1-Dichloroethene did not induce micronuclei in bone marrow of mice following gavage administration or in fetal liver or blood following intraperitoneal administration to pregnant mice (Sawada et al. 1987). 1,1-Dichloroethene inhalation was associated with low rates of DNA alkylation in the livers and kidneys of mice and rats (Reitz et al. 1980). DNA repair mechanisms were induced in the kidney cells of mice in which normal replicative DNA synthesis had

been inhibited, but apparently not in mouse liver nor kidneys or liver of rats (Reitz et al. 1980). Negative results were reported in assays for dominant lethal mutations in mice (Andersen et al. 1977) and rats (Short et al. 1977c). In a mouse host-mediated assay system, 1,1-dichloroethene induced gene mutation and gene conversion in yeast (Bronzetti et al. 1981).

Table 2-5. Genotoxicity of 1,1-Dichloroethene *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
Non-mammalian cells:			
Drosophila melanogaster male germ cells (feeding or injection)	Sex-linked recessive lethal mutations	–	NTP 2015a
Mammalian cells:			
Rat bone marrow (inhalation)	Chromosomal aberrations	–	Rampy et al. 1977
Mouse peripheral blood erythrocytes (inhalation)	Micronuclei	–	NTP 2015a
Mouse bone marrow (gavage)	Micronuclei	–	Sawada et al. 1987
Mouse fetal liver and blood (gavage)	Micronuclei	–	Sawada et al. 1987
Mouse kidney (inhalation)	DNA damage	(+)	Reitz et al. 1980
Mouse (inhalation)	Dominant lethality	–	Andersen et al. 1977
Rat (inhalation)	Dominant lethality	–	Short et al. 1977c
Host-mediated assays:			
Saccharomyces cerevisiae D7 in CD mouse host treated by gavage	Gene mutation	+	Bronzetti et al. 1981
S. cerevisiae D7 in CD mouse host treated by gavage	Gene conversion	+	Bronzetti et al. 1981

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

2.21 MECHANISMS OF ACTION

Available human data are inadequate to assess mechanisms of action for 1,1-dichloroethene. However, the general toxicokinetics of 1,1-dichloroethene are expected to be similar between humans and animals. Based on available animal data, nasal tissues, liver, and kidney are major targets of 1,1-dichloroethene toxicity associated with inhalation exposure. The liver and kidney are major toxicity targets associated with oral exposure.

No information was located regarding potential mechanisms of action for nasal effects associated with inhalation exposure to 1,1-dichloroethene in rats and mice.

In laboratory animals, the mechanism of 1,1-dichloroethene lung, liver, and kidney toxicity is related to production of reactive metabolites (see Section 3.1.3). In the liver, 1,1-dichloroethene undergoes CYP2E1-catalyzed metabolism to the reactive intermediates 1,1-dichloroethene epoxide and 2-chloroacetyl chloride, and 2,2-dichloroacetaldehyde. These reactive intermediates (presumed hepatic toxicants) undergo conjugation by GSH or cysteine, followed by transportation to the kidney (Ban et al. 1995). The proposed mechanism for 1,1-dichloroethene kidney toxicity is associated with β-lyase bioactivation of hepatic GSH conjugates and/or their derivatives to reactive species (Ban et al. 1995; Cavelier et al. 1996; Dekant et al. 1989; Lash et al. 2000). Eyre et al. (1995) demonstrated that β-lyase bioactivation of trichloroethylene was greater in mice than rats; this finding is consistent with increased sensitivity of the mouse kidney to 1,1-dichloroethene toxicity. Increased sensitivity of male mice (compared to female mice) to 1,1-dichloroethene renal toxicity has been attributed to increased rates of 1,1-dichloroethene oxidation in the male kidney (Speerschneider and Dekant 1995).

Forkert and coworkers (reviewed by Forkert 2001) identified bronchiolar Clara cells (club cells) and centrilobular hepatocytes as targets of 1,1-dichloroethene metabolites formed via CYP2E1-catalyzed oxidation in mice and humans. Simmonds et al. (2004) demonstrated that CYP2E1 was the principal high-affinity enzyme involved in the bioactivation of 1,1-dichloroethene in the murine lung, but that CYP2F2 was involved as well. Dowsley et al. (1996) identified 1,1-dichloroethene epoxide (in the form of two glutathione conjugates) as the major metabolite formed in murine lung microsomal incubations and implicated the epoxide as an important mediator of 1,1-dichloroethene-induced lung cytotoxicity.

Nakahama et al. (2001) evaluated the mode of action of 1,1-dichloroethene on expression of rat CYP forms and concluded that 1,1-dichloroethene suppresses the induction of hepatic CYP2B and 2E1 in advance of the transcriptional stage. Martin and Forkert (2005) demonstrated that mitochondrial damage precedes apoptotic cell death of bronchiolar epithelial cells from mice administered 1,1-dichloroethene by intraperitoneal injection at 75 mg/kg.

Dose-dependent increases in renal cell hyperplasia, renal cell adenoma, and renal cell carcinomas were observed in male B6C3F1/N mice intermittently exposed to 1,1-dichloroethene vapor for up to 2 years (NTP 2015a). Hayes et al. (2016) demonstrated that the renal cell carcinomas were characterized by oxidative stress and tumor suppressor gene (TP53) pathway dysregulation.

Possible mechanisms responsible for increased susceptibility to 1,1-dichloroethene toxicity in fasted animals have been studied. Jaeger et al. (1973a) demonstrated that fasted rats exhibited depleted hepatic GSH and increased susceptibility to 1,1-dichloroethene hepatotoxicity. Hepatic GSH levels diminished during the inactive/sleep cycle (lack of food intake), making them more susceptible to 1,1-dichloroethene hepatotoxicity. GSH acts by detoxifying electrophilic 1,1-dichloroethene metabolites. Bruckner et al. (2002) evaluated the diurnal rhythm in rats and its relationship to metabolism of the chlorinated hydrocarbon, carbon tetrachloride, and found that lack of food intake during the inactive/sleep cycle not only depressed GSH levels, but also resulted in CYP2E1 induction. Depletion of GSH in concert with CYP2E1 induction significantly increased metabolic activation and suppressed its inactivation.

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

3.1 TOXICOKINETICS

Data regarding toxicokinetics of 1,1-dichloroethene in humans are not available. Toxicokinetic studies in animals indicate the following:

- Inhaled or ingested 1,1-dichloroethene is readily absorbed through the lung and by the gastrointestinal tract.
- Following absorption, 1,1-dichloroethene and its metabolites are rapidly distributed by the blood; particular toxicity targets include the liver and kidney.
- 1,1-Dichloroethene is metabolized by the hepatic microsomal cytochrome P450 system to reactive metabolites; detoxification of reactive metabolites occurs primarily via epoxide hydrolase/hydrase-catalyzed hydrolysis and conjugation with GSH.
- Excretion of metabolites occurs primarily via the urine and exhaled air; unmetabolized parent compound may also be eliminated in exhaled air.

3.1.1 Absorption

No studies were located regarding absorption of 1,1-dichloroethene in humans.

Studies in laboratory animals demonstrate that inhaled 1,1-dichloroethene is rapidly absorbed (Dallas et al. 1983; McKenna et al. 1978a). The observation that rats exhibited a higher body burden than mice following similar exposure to 1,1-dichloroethene vapor indicates that species-specific differences may exist in the rate and/or extent of absorption (McKenna et al. 1977). No studies were located that described transport mechanisms for 1,1-dichloroethene absorption. Since 1,1-dichloroethene is a small organic molecule with chemical and physical properties similar to those of lipid soluble anesthetics, it is expected to penetrate pulmonary membranes easily and to enter the bloodstream rapidly. Substantial levels of the parent compound were found in the venous blood of rats within 2 minutes after inhalation exposure (Dallas et al. 1983). Absorption of 1,1-dichloroethene was duration- and dose-dependent. The percentage of systemic uptake decreased with time from the onset of exposure until an equilibrium was reached within 1 hour. Once equilibrium was reached, percentage uptake varied inversely with dose. The cumulative uptake of 1,1-dichloroethene following inhalation exposure was linear for levels ≤150 ppm. However, at 300 ppm, a steady state was never achieved. This finding indicates that 1,1-dichloroethene

absorption following inhalation exposure was saturable at high levels, and the kinetics at these levels are best described by a cubic curve (Dallas et al. 1983).

Studies in animals clearly indicate that oral doses of 1,1-dichloroethene (in corn oil) ranging from 10 to 100 mg/kg are rapidly and almost completely absorbed from the gastrointestinal tract of rats and mice (Jones and Hathway 1978a; Putcha et al. 1986). Rapid absorption occurred following oral administration of 200 mg/kg in an aqueous emulsion, as evidenced by the observation that the largest percentage of the dose was exhaled during the initial 15-minute period (Chieco et al. 1981). Peak blood levels were achieved in rats within 2–8 minutes after oral administration (Putcha et al. 1986). When 0.5–50 mg/kg of radiolabeled 1,1-dichloroethene was given to female rats, approximately 10% of the parent compound was recovered in the expired air by 1 hour after exposure, indicating that oral absorption was rapid (Reichert et al. 1979). After oral administration to rats of 1,1-dichloroethene labeled with radioactive carbon (^{14}C), 81–99.8% of the administered radioactivity was recovered within 72 hours (Reichert et al. 1979). Studies have shown that 9–21% was recovered in the expired air, 53.9% in urine, 14.5% in feces, 2.8% in the carcass, and 7.5% in the cage rinse following oral administration of 1 or 5 mg ^{14}C-1,1-dichloroethene/kg (McKenna et al. 1978b; Reichert et al. 1979). After a dose of 50 mg ^{14}C-1,1-dichloroethene/kg, 19 and 29% of the parent compound was excreted via lungs in nonfasted and fasted rats, respectively (McKenna et al. 1978b).

No studies were located regarding absorption in animals after dermal exposure to 1,1-dichloroethene. Nonetheless, the physical/chemical properties of 1,1-dichloroethene indicate that dermal absorption of 1,1-dichloroethene is probable. 1,1-Dichloroethene is a small organic molecule with properties similar to that of lipid-soluble anesthetics. Thus, liquid 1,1-dichloroethene is expected to readily penetrate the skin, which is a lipid-rich tissue. However, with a vapor pressure of 600 mmHg at 25°C, the rate of evaporation would be rapid leaving only a short time for skin penetration.

3.1.2 Distribution

No studies were located regarding distribution of 1,1-dichloroethene in humans.

Following inhalation exposure of rats to 10 or 200 ppm of ^{14}C-labeled 1,1-dichloroethene, the highest level of radioactivity was found in the liver and kidneys after 72 hours, with only very small amounts present in other tissues (McKenna et al. 1978a). These authors found that the tissue burden/g of tissue (mg equivalents of ^{14}C-1,1-dichloroethene/g of tissue/total mg equivalents recovered per rat) in the liver,

kidneys, and lungs of fasted rats was significantly greater than the tissue burden in nonfasted rats at both exposure levels, even though the total accumulation of ^{14}C in fasted rats was less than that of nonfasted rats. The results of this study suggest the nonrandom retention of parent compound and/or metabolites in specific target tissues of fasted animals.

Preferential accumulation of radioactivity was reported in the kidney and liver of rats exposed to radiolabeled 1,1-dichloroethene vapor for 2 hours at 2,000 ppm (Jaeger et al. 1977). Higher levels of radioactivity were noted in liver and kidney from fasted rats than from nonfasted rats. Examination of ^{l4}C activity at the subcellular level in these two tissues revealed that significantly more water-soluble ^{14}C activity was present in the cytosolic fractions of fasted rats. This observation suggests that distribution pathways for metabolism differ according to the amount of food ingested.

1,1-Dichloroethene was rapidly distributed to all tissues examined following a single oral dose of the ^{14}C-labeled compound to rats (Jones and Hathway 1978c). The highest amount of radioactivity was found in the liver and kidneys within 30 minutes of administration. More general redistribution throughout the soft tissues of the body followed.

No studies were located regarding distribution after dermal exposure to 1,1-dichloroethene.

In a study by Okine et al. (1985) in which mice were administered a single intraperitoneal injection of 125 mg/kg of ^{14}C-1,1-dichloroethene, radioactivity was distributed to some extent to all examined tissues, with peak levels seen 6 hours after administration. The highest levels of radioactivity were found in the kidney, liver, and lung, with lesser amounts in the skeletal muscle, heart, spleen, and gut.

3.1.3 Metabolism

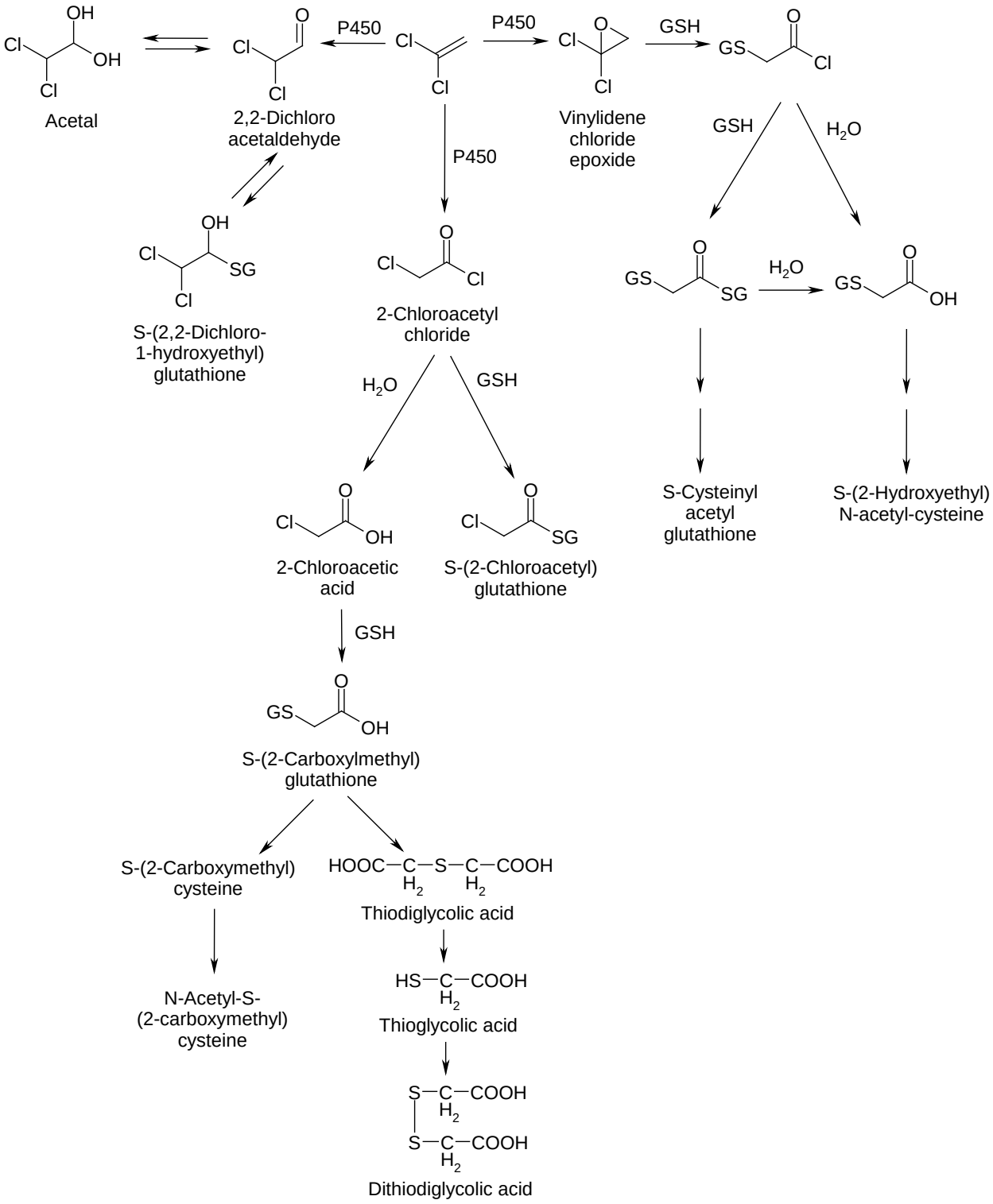
The metabolism of 1,1-dichloroethene following oral administration in rats has been extensively studied (Jones and Hathway 1978a, 1978c; McKenna et al. 1978b; Reichert et al. 1979). These studies demonstrate that 1,1-dichloroethene undergoes extensive biotransformation, and several metabolites have been identified. Results from *in vitro* assays using human tissues provide evidence for similarities between animals and humans in 1,1-dichloroethene metabolism (Dowsley et al. 1999). The cytochrome P450 CYP2E1 isozyme has been demonstrated to catalyze the formation of the 1,1-dichloroethene epoxide in both animal and human tissues (Dowsley et al. 1996; Speerschneider and Dekant 1995). The finding that liver cells from a human subject, together with Arochlor-pretreated S9-activated

1,1-dichloroethene, induced unspecified mutagenic metabolites in a *S. typhimurium* assay (Jones and Hathway 1978b) suggests that reactive metabolites may be produced in humans.

Proposed metabolic pathways for 1,1-dichloroethene are presented in Figure 3-1. According to the metabolic scheme, 1,1-dichloroethene undergoes P450-catalyzed epoxidation or oxidation to form the electrophilic metabolites 1,1-dichloroethene epoxide, 2-chloroacetyl chloride, and 2,2-dichloro-acetaldehyde. In rats, the oxidative metabolism of 1,1-dichloroethene reached saturation at an inhalation exposure level of approximately 200 ppm and an oral exposure of 10–50 mg/kg (Andersen et al. 1979; Dallas et al. 1983; D'Souza and Andersen 1988; McKenna et al. 1977). The reactive metabolites of 1,1-dichloroethene undergo hydrolysis and react with glutathione and cellular macromolecules. The observation that GSH is depleted in the liver following exposure to 1,1-dichloroethene suggests the importance of GSH conjugation as a major pathway in the detoxification of the reactive 1,1-dichloro-ethene metabolites (Jaeger et al. 1974; Reichert et al. 1978; Reynolds et al. 1980). Reynolds et al. (1980) reported a linear relationship in rats between intraperitoneally administered 1,1-dichloroethene and GSH depletion over the range of 20–100 mg/kg; above this level, GSH depletion reached a plateau. The maximum reduction (70%) occurred 4 hours after treatment, with a subsequent gradual recovery to normal levels within 24 hours. These findings led several investigators to suggest that 1,1-dichloro-ethene-induced hepatotoxicity is related to the depletion of hepatic GSH levels, thereby permitting the reactive intermediate to covalently bind to and alkylate hepatic macromolecules instead of being detoxified, ultimately leading to cell death (Jaeger et al. 1974; McKenna et al. 1977, 1978b; Reynolds et al. 1980).

Several 1,1-dichloroethene urinary and biliary metabolites have been identified in animal studies (Costa and Ivanetich 1982; Dowsley et al. 1995; Forkert 1999a, 1999b; Jones and Hathway 1978a, 1978c; Jones et al. 2003; Liebler et al. 1985, 1988; Okine and Gram 1986; Okine et al. 1985; Simmonds et al. 2004). Urinary metabolites include *N*-acetyl-*S*-(2-hydroxyethyl) cysteine, *S*-(cysteinyl acetyl) glutathione, *N*-acetyl-*S*-(2-carboxymethyl) cysteine, thiodiglycolic acid, dithioglycolic acid, dithiodiglycolic acid, and chloroacetic acid. Biliary metabolites include *S*-(2-carboxymethyl) glutathione, *S*-(cysteinyl acetyl) glutathione, several carboxymethylated proteins, and a product of the intramolecular rearrangement of the metabolite, *S*-(2-chloroacetyl)glutathione.

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



Source: NTP 2015a

The pathways of 1,1-dichloroethene metabolism in the mouse were generally similar to pathways in the rat, although several differences were observed. The rate of metabolism was greater in the mouse (Dowsley et al. 1995; Jones and Hathway 1978a). A predominant urinary metabolite of 1,1-dichloroethene in the mouse was *N*-acetyl-*S*-(2-carboxymethyl) cysteine; this metabolite was not detected in rat urine. The mouse produced a higher proportion of urinary S-(2-hydroxyethyl)-N-acetyl cysteine (a product of the reaction between 1,1-dichloroethene epoxide and GSH), suggesting a greater rate and/or extent of formation of 1,1-dichloroethene epoxidation in the mouse. Quantitatively greater amounts of other (water-soluble) urinary metabolites were present in the mouse urine (and consequently less parent compound in the expired air), attesting to a greater metabolic capacity. Furthermore, β-thionase activity was more pronounced in the mouse since more dithioglycolic acid was found than thiodiglycolic acid (Jones and Hathway 1978a). Oesch et al. (1983) suggested that 1,1-dichloroethene may have different effects on cytosolic GSH transferase activity and that this difference may contribute to species differences in 1,1-dichloroethene metabolism.

Forkert and Boyd (2001) evaluated hepatic metabolism of 1,1-dichloroethene in three different strains of mice (A/J, CD-1, and C57Bl/6). The A/J strain exhibited the highest level of hepatic CYP2E1, the greatest extent of covalent binding of 1,1-dichloroethene to liver proteins, and the highest level of 1,1-dichloroethene epoxide-derived glutathione conjugate in liver cytosol. These findings correlated well with the greater degree of 1,1-dichloroethene-induced centrilobular necrosis in the A/J strain compared to the CD-1 and C57Bl/6 strains.

1,1-Dichloroethene metabolism has been studied in a variety of *in vitro* tests. 1,1-Dichloroethene epoxide was the major metabolite produced in rat liver and mouse liver and lung microsomal incubations; minor metabolites included 2,2-dichloroacetaldehyde and 2-chloroacetylchloride (Costa and Ivaneitch 1982; Dowsley et al. 1995, 1996; Forkert 2001; Liebler and Guengerich 1983; Liebler et al. 1985; Simmonds et al. 2004). Secondary reactions included oxidation, glutathione conjugation, and hydrolysis. Dowsley et al. (1999) demonstrated that human lung and liver microsomal preparations exposed to 1,1-dichloroethene produced 1,1-dichloroethene epoxide as a major metabolite and that the reaction was catalyzed by CYP2E1. Simmonds et al. (2004) evaluated 1,1-dichloroethene metabolism in incubated mouse lung microsomes, and recombinant rat and human CYP2E1, mouse CYP2F2, goat CYP2F3, and rat CYP2F4. The recombinant rat CYP2E1 exhibited the greatest affinity and catalytic efficiency for 1,1-dichloroethene, suggesting a possible basis for species-specific differences in sensitivity to 1,1-dichloroethene liver and kidney toxicity.

1,1-Dichloroethene covalently binds preferentially to liver and kidney tissues following administration, which may provide a basis for the toxic effects seen in these organs (Jaeger et al. 1977; McKenna et al. 1977, 1978b). A linear increase in the amount of covalently bound radioactivity in the liver of rats exposed to 10–200 ppm ^{14}C-1,1-dichloroethene by inhalation for 6 hours was reported by McKenna et al. (1977). However, GSH depletion approached saturation at about 200 ppm. Therefore, the actual amount of reactive metabolite formed and available for binding was probably determined by a combination of both activation and detoxification pathways.

The increased severity of nephrotoxic effects induced by 1,1-dichloroethene in the mouse, compared to the rat, may be partially explained by the observation that the level of covalently bound reactive material in the mouse kidney was 6 times higher than the level in the rat kidney following similar inhalation exposure of both species (McKenna et al. 1977). This observation might also explain the increased severity of hepatic effects in the mouse compared to the rat. Similar results were reported by Short et al. (1977a) when a single dose of ^{14}C-1,1-dichloroethene was injected intraperitoneally into mice. The highest level of covalently bound radioactivity was seen in the mouse kidney. The study authors found that pretreatment with disulfiram also reduced the amount of covalent binding. The study authors speculated that disulfiram may reduce the activation of 1,1-dichloroethene and increase the extent of its detoxification. The inhibition of CYP2E1 by disulfiram has been demonstrated by Guengrich et al. (1991) and Yamazaki et al. (1992). Thus, conjugation of reactive intermediates of 1,1-dichloroethene with GSH is a major detoxification mechanism in laboratory animals because it reduces the amount of reactive material available to covalently bind to cellular macromolecules.

3.1.4 Excretion

No studies were located regarding excretion in humans exposed to 1,1-dichloroethene. Available animal data demonstrate that elimination is relatively rapid following inhalation or oral exposure.

Following inhalation exposure of rats to low levels of 1,1-dichloroethene elimination is rapid, mostly as metabolites in the urine, and very little (1% of the administered dose) eliminated as the unchanged parent compound in the expired air (McKenna et al. 1977). After exposure to low levels (25–150 ppm) of 1,1-dichloroethene, steady-state levels of 1,1-dichloroethene in the expired air are achieved within 30–45 minutes, indicating that elimination is first-order at low levels of exposure (Dallas et al. 1983). Steady-state levels of 1,1-dichloroethene in expired air are never reached when exposure levels approach 200–300 ppm because metabolic processes are saturated. When metabolic processes become saturated,

increased amounts of 1,1-dichloroethene can easily be eliminated unchanged via the expired air because 1,1-dichloroethene is volatile (vapor pressure of 600 mmHg at 25°C) and relatively insoluble in blood. Following cessation of exposure, concentrations of 1,1-dichloroethene in both blood and breath were observed to fall rapidly (Dallas et al. 1983). Similar results were reported by McKenna et al. (1978a).

1,1-Dichloroethene exhibited a biphasic elimination profile following inhalation exposure in rats (McKenna et al. 1977, 1978a). For the first phase, elimination half-lives were about 20 minutes for unchanged 1,1-dichloroethene in breath and 3 hours for water-soluble metabolites in urine. For the second phase, elimination half-lives were about 4 hours in breath and 20 hours in urine. The bulk of the material was eliminated in both the breath and the urine during the rapid first phase. Fasting did not appear to affect the elimination kinetics of 1,1-dichloroethene following inhalation exposure in rats (McKenna et al. 1978a). Bruckner et al. (2010) evaluated the plasma kinetics of 1,1-dichloroethene in fasted Sprague-Dawley rats. Following inhalation exposure at 300 ppm, the elimination half-life was 50 minutes.

Information is limited on elimination in mice following inhalation exposure to 1,1-dichloroethene. However, McKenna et al. (1977) reported that at low levels of exposure (10 ppm for 6 hours), somewhat smaller amounts of unchanged 1,1-dichloroethene were eliminated in the expired air of mice and larger amounts of water-soluble metabolites were found in the urine of mice compared to levels observed in rats. This indicates that mice metabolize 1,1-dichloroethene at a greater rate than rats.

Elimination of 1,1-dichloroethene and its metabolites following oral administration in rats is very similar to that seen following inhalation exposure. Following oral administration of 1 mg/kg ^{14}C-1,1-dichloroethene in corn oil, <1% of the administered dose was excreted unchanged in the expired air; another 8–14% was recovered as ^{14}C-carbon dioxide. Most of the radioactivity (44–80% of the administered dose) was eliminated in the urine within 3 days, most within the first 24 hours. Smaller amounts of water-soluble metabolites (8–16% of the administered dose) were found in the feces (Jones and Hathway 1978c; McKenna et al. 1978b; Reichert et al. 1979). Following the oral administration of higher doses to rats (50 mg/kg ^{14}C-1,1-dichloroethene), a higher proportion of unchanged parent compound (16–30% of the administered dose) was excreted in the breath, with a concomitant reduction in the amount of expired carbon dioxide (3–6% of the administered dose) and urinary metabolites (35–42% of the administered dose) (Jones and Hathway 1978c; McKenna et al. 1978b; Reichert et al. 1979). Similar, but more marked, trends were observed at even higher doses (Chieco et al. 1981; Jones and Hathway 1978c). Thus, metabolic processes become saturated at rather low dose levels.

The elimination of orally administered 1,1-dichloroethene is triphasic according to Putcha et al. (1986); however, McKenna et al. (1978a) and Reichert et al. (1979) reported that elimination is biphasic. The first phase identified by Putcha et al. (1986) occurred almost immediately, within the first few minutes after exposure, and the subsequent two phases corresponded to those observed by the other investigators.

The amount of food ingested in the previous 24 hours slightly modifies the elimination of 1,1-dichloroethene by rats after oral administration. It was found that 19 and 29% of a 50 mg/kg dose was excreted unchanged via the lungs of nonfasted and fasted rats, respectively (McKenna et al. 1978a). This finding provides suggestive evidence that unchanged 1,1-dichloroethene may be eliminated to a greater extent from fasted rats. However, elimination of nonvolatile metabolites was slightly greater in nonfasted animals than in fasted animals, indicating a reduced capacity for metabolism in fasted rats.

At comparable doses, mice eliminate more 1,1-dichloroethene as water-soluble metabolites in the urine than rats (Jones and Hathway 1978a). These results indicate that orally administered 1,1-dichloroethene is metabolized to a greater extent in mice than rats.

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.

D'Souza and Andersen (1988) developed PBPK models for inhalation and oral exposure of rats to 1,1-dichloroethene. There is no validated model for humans. Allometric scaling was employed to estimate amounts of epoxide formed in rats and humans. Cardiac output and ventilation rates were scaled by body weight. For oral exposures at <5 mg/kg, the model estimated comparable amounts of epoxide formation for rats and humans. At inhalation exposure levels <100 ppm, estimates of epoxide formation

for humans were 5-fold higher than those in those for rats. This model is not useful for human health risk assessment due to the lack of a validated human model.

El-Masri et al. (1996a, 1996b) assessed the potential for competitive inhibition between trichloroethylene and 1,1-dichloroethene using results from gas uptake experiments in rats and physiologically based pharmacodynamic (PBPD) modeling. The model descriptions of hepatic GSH kinetics were calibrated against published data and gas uptake experiments. The model was used to identify the critical time point at which GSH is at a minimum. According to the combination of gas uptake experiments and PBPD modeling, 1,1-dichloroethene, but not trichloroethylene, was capable of significantly depleting hepatic GSH. At exposure concentrations higher than 100 ppm (but not <100 ppm), trichloroethylene obstructed the ability of 1,1-dichloroethene to deplete hepatic GSH. Thus, trichloroethylene exposure concentrations >100 ppm are predicted to competitively inhibit GSH-mediated metabolism of 1,1-dichloroethene to its epoxide. This model is not useful for human health risk assessment.

3.1.6 Animal-to-Human Extrapolations

Studies in rats and mice demonstrate rapid absorption following inhalation or oral exposure to 1,1-dichloroethene (Dallas et al. 1983; Jones and Hathway 1978a; McKenna et al. 1978a; Putcha et al. 1986). Absorbed 1,1-dichloroethene, its metabolites, and covalently bound derivatives are found in the liver and kidney (Jaeger et al. 1977; Jones and Hathway 1978c; McKenna et al. 1978a). In animals, 1,1-dichloroethene is rapidly oxidized by CYP2E1 to three initial metabolites (1,1-dichloroethene epoxide, 2-chloroacetyl chloride, and 2,2-dichloroacetaldehyde) (Jones and Hathway 1978a, 1978c; McKenna et al. 1978b; Reichert et al. 1979). The extent of similarities between animals and humans regarding metabolism of 1,1-dichloroethene is not known. However, human and rodent *in vitro* microsomal preparations form the same initial 1,1-dichloroethene metabolites, including 1,1-dichloroethene epoxide (the metabolite of major cytotoxic and mutagenic concern) (Dowsley et al. 1996, 1999).

The toxicity of 1,1-dichloroethene has been studied in acute-, intermediate-, and chronic-duration inhalation and oral studies. Critical targets of toxicity in rats and mice exposed by inhalation are nasal epithelium, liver, and kidney, as demonstrated in intermediate- and chronic-duration studies of both species (NTP 2015a). Rats appear to be more sensitive than mice to nasal and hepatic effects; mice appear to be more sensitive than rats to kidney effects. Limited data regarding species differences in

sensitivity to 1,1-dichloroethene toxicity do not indicate significant species differences in 1,1-dichloroethene toxicity following oral exposure.

Human toxicokinetic and toxicity data for 1,1-dichloroethene are lacking. Available rat and mouse data indicate significant species differences. There are insufficient data to assess which species would represent the best model for human toxicity. Therefore, for purposes of human health hazard assessment, the species exhibiting the most sensitive endpoint considered relevant to humans is considered the most conservative approach to derivation of MRLs for 1,1-dichloroethene.

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

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

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

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

Specific information regarding human subpopulations, including infants and children, that are unusually susceptible to the toxic effects of 1,1-dichloroethene were not located. However, results from animal studies suggest that certain populations may exhibit increased sensitivity to 1,1-dichloroethene toxicity.

The liver mixed function oxidase (MFO) activity in fasted animals or animals kept on a low carbohydrate diet was enhanced when exposed to 1,1-dichloroethene, compared to that in similarly exposed control (carbohydrate-fed) animals (McKenna et al. 1978b; Nakajima et al. 1982). Fasting prior to 1,1-dichloro-ethene exposure resulted in an earlier appearance of hepatic lesions, a more extensive distribution of

lesions, and a reduced ability to metabolize high doses of 1,1-dichloroethene when compared to control (nonfasted) rats (Jaeger et al. 1974; McKenna et al. 1978b; Reynolds and Moslen 1977).

Sex differences in the toxic response to 1,1-dichloroethene were observed in animals. For example, in a chronic inhalation exposure study in rats, hepatotoxic effects occurred at lower 1,1-dichloroethene concentrations in female rats than in male rats (25 and 75 ppm, respectively) (Quast et al. 1986). Fasted male animals, particularly young males, appear to be more susceptible to the toxic effects of 1,1-dichloroethene than fasted females, as evidenced by their enhanced responses at lower doses of 1,1-dichloroethene.

Individuals with high levels of CYP2E1 such as abusers of ethanol and those routinely exposed to other substances that induce CYP2E1 might be at increased risk of 1,1-dichloroethene toxicity. Individuals with low levels of GSH (e.g., individuals malnourished or fasting and those taking acetaminophen) might also be at increased risk of 1,1-dichloroethene toxicity. Phenobarbital, even though somewhat protective against 1,1-dichloroethene-generated liver damage (Carlson and Fuller 1972), sensitized the heart to 1,1-dichloroethene-induced arrhythmias (Siletchnik and Carlson 1974). Since phenobarbital is sometimes used as a soporific, and by those with various forms of epilepsy or seizure disorders, people who are taking this medication or those with pre-existing arrhythmic heart conditions should not be exposed to high levels of 1,1-dichloroethene. Thyroidectomy, either chemical or surgical, can protect against the hepatotoxicity associated with inhalation of 1,1-dichloroethene. Conversely, thyroxine treatment to replace or supplement normal thyroid function increases the amount of liver damage upon subsequent exposure to 1,1-dichloroethene in animals (Szabo et al. 1977). Individuals with liver or kidney disease or those with an acute hypersensitivity to 1,1-dichloroethene should avoid exposure to 1,1-dichloroethene.

Specific data concerning teratogenicity in humans exposed to 1,1-dichloroethene were not found in the literature. 1,1-Dichloroethene has been described as a possible teratogen responsible for soft-tissue anomalies in rats and skeletal defects in mice, rats, and rabbits, often at levels that produced clear evidence of toxicity in the dam.

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, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to 1,1-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 1,1-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 1,1-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

There are limited data on biomarkers of 1,1-dichloroethene exposure. Halogenated solvents, including 1,1-dichloroethene, measured in blood reflect recent exposure (CDC 2017). Blood 1,1-dichloroethene levels were used to evaluate exposure in samples collected from National Health and Nutrition Examination Survey (NHANES) participants. Toxicokinetic studies in animals have identified 1,1-dichloroethene and a number of 1,1-dichloroethene metabolites in blood and urine and parent compound in expired air (Dallas et al. 1983; McKenna et al. 1977, 1978a). Since 1,1-dichloroethene and

its metabolites are rapidly eliminated from the body (Bruckner et al. 2010; Dallas et al. 1983; McKenna et al. 1978a), measurements of biomarker levels would only be indicative of recent exposure. Furthermore, some of the metabolites may be formed following exposure to other chlorinated substances as well.

3.3.2 Biomarkers of Effect

The liver and kidney are primary target organs for 1,1-dichloroethene exposure. Inhalation exposure to 50 ppm 1,1-dichloroethene was associated with minimal rates of DNA alkylation in liver and kidney cells of laboratory rats and mice (Reitz et al. 1980). Exposure to 1,1-dichloroethene (depending on dose and duration of exposure) increases serum levels of certain liver enzymes such as AST, ALT, and others, which is taken as an indication of liver injury. However, these effects are caused by other halogenated alkenes as well, such as vinyl chloride, and cannot be considered as a specific indicator of 1,1-dichloroethene effects.

3.4 INTERACTIONS WITH OTHER CHEMICALS

As discussed in previous sections, it is apparent that the toxicity of 1,1-dichloroethene is largely due to the formation of toxic intermediates during metabolism *in vivo*. The production and biotransformation of toxic metabolic intermediates of 1,1-dichloroethene can be greatly influenced by various metabolic inhibitors and inducers, and by the availability of precursors of compounds involved in detoxification, such as GSH.

Microsomal MFOs are a group of enzymes involved in the biotransformation and detoxication of xenobiotics such as 1,1-dichloroethene. Inhibitors of some microsomal MFOs include the compound SKF-525-A, disulfiram, and other dithiocarbamates, such as thiram and diethyldithiocarbamate. These compounds reduce the toxic effects of 1,1-dichloroethene in the liver, probably by inhibiting the enzymes responsible for the formation of reactive toxic intermediates (Masuda and Nakayama 1983; Short et al. 1977b). Pretreatment with intracellular cysteine precursor, L-2-oxothiazolidine-4-carboxylate, is also used to protect against 1,1-dichloroethene toxicity (Moslen et al. 1989a). Cysteine precursors enhance GSH levels, thus promoting detoxification of toxic 1,1-dichloroethene intermediates. Inhibitors of metabolic enzymes responsible for the breakdown of reactive 1,1-dichloroethene intermediates may also enhance the toxicity of 1,1-dichloroethene. For example, 1,1,1-trichloropropane and other inhibitors of epoxide hydrolase can potentiate the toxicity of 1,1-dichloroethene (Jaeger 1977). It should be noted, however, that substances such as 1,1,1-trichloropropene-2,3-oxide may inhibit CYP450 isozymes

involved in biotransformation and detoxification as well (Ivanetich et al. 1982). Other chemicals that reduce the activity of metabolic enzymes and show some protective effects against the toxicity of 1,1-dichloroethene include pyrazole, and 3-aminotriazol (Andersen et al. 1978).

Pretreatment of rats with acetaminophen greatly increased lethality and the hepatotoxic effects of 1,1-dichloroethene (Wright and Moore 1991). Although the depletion of GSH was not discussed, the study authors concluded that acetaminophen produces alterations that make hepatocytes more susceptible to 1,1-dichloroethene injury.

Enzyme inducers may either protect against or exacerbate the toxicity of 1,1-dichloroethene. Induction of enzymes involved in the formation of toxic intermediates potentiates 1,1-dichloroethene-induced toxicity following 1,1-dichloroethene exposure; conversely, induction of enzymes responsible for the biodegradation of the toxic intermediate(s) decreases toxicity. Examples of compounds that induce MFOs and increase toxic effects upon exposure to 1,1-dichloroethene include ethanol and acetone (Charbonneau et al. 1991; Hewitt and Plaa 1983; Kainz et al. 1993; Sato et al. 1983). In acetone-pretreated rats, mixtures containing chloroform or carbon tetrachloride plus 1,1-dichloroethene increased hepatotoxic responses additively (Charbonneau et al. 1991).

Many inducers of MFO enzymes do not increase the hepatotoxicity of 1,1-dichloroethene, apparently because they stimulate enzyme systems not involved in the metabolism of 1,1-dichloroethene. An example of a P450 inducer is phenobarbital (Carlson and Fuller 1972). Jenkins et al. (1972) found that pretreatment of rats with phenobarbital followed by oral administration with 1,1-dichloroethene had a protective effect against liver damage, while Carlson and Fuller (1972) found that pretreatment of rats with phenobarbital followed by inhalation exposure to 1,1-dichloroethene increased mortality but had no effect on hepatotoxicity. This discrepancy may be due to differences in routes of administration and indicators of toxicity examined.

Thyroidectomy protected rats from the hepatotoxic effects of 1,1-dichloroethene, probably by increasing the amount of hepatic GSH (Szabo et al. 1977). Other studies have also reported increases in hepatic GSH in thyroidectomized rats (e.g., Teare et al. 1993). Thyroxine replacement in thyroidectomized rats exacerbated the liver damage seen upon subsequent exposure to 1,1-dichloroethene (Szabo et al. 1977).

Pretreatment of animals with compounds that deplete GSH levels (such as buthionine sulfoximine) increased the amount of liver damage caused by 1,1-dichloroethene exposure (Reichert et al. 1978).

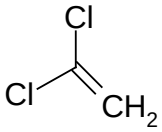
Conversely, pretreatment of animals with supplements containing high concentrations of the amino acids cysteine and/or methionine, both of which are metabolic contributors of the sulfhydryl group required for GSH biosynthesis, had a protective effect against the toxicity of 1,1-dichloroethene (Short et al. 1977a).

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Table 4-1 lists common synonyms and other identification information for 1,1-dichloroethene.

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

Characteristic	Information	Reference
Chemical name	1,1-Dichloroethene	NLM 2018
Synonym(s) and registered trade name(s)	1,1-DCE; 1,1-dichloroethylene; asym-dichloroethylene; VDC; vinylidene chloride; vinylidene chloride (II); vinylidene dichloride; vinylidene chloride	NLM 2018; EPA 2017a; NIOSH 2016
Chemical formula	$C_2H_2Cl_2$	EPA 2017a
Chemical structure		NLM 2018
CAS Registry Number	75-35-4	EPA 2017a

CAS = Chemical Abstracts Service

4.2 PHYSICAL AND CHEMICAL PROPERTIES

1,1-Dichloroethene is a colorless, volatile liquid at room temperature, has a mild, sweet odor, is flammable, and burns quickly. This chemical readily polymerizes, and commercial products therefore typically contain an inhibitor (Larranaga et al. 2016). 1,1-Dichloroethene does not occur naturally in the environment; it is produced commercially from ethylene chloride. The major use for 1,1-dichloroethene is in the synthesis of various industrial and consumer plastics, such as packaging materials and flexible films (O'Neil et al. 2013). It also has reported use as a filler, binding agent, and adhesive in paints and synthetic fibers (Larranaga et al. 2016). Effective as of August 15, 2000, 1,1-dichloroethene is categorized as a volatile organic compound (VOC) (EPA ID: E761502) and hazardous air pollutant (HAP) (EPA ID: E761346) (EPA 2017b).

Physical and chemical properties of 1,1-dichloroethene are listed in Table 4-2.

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

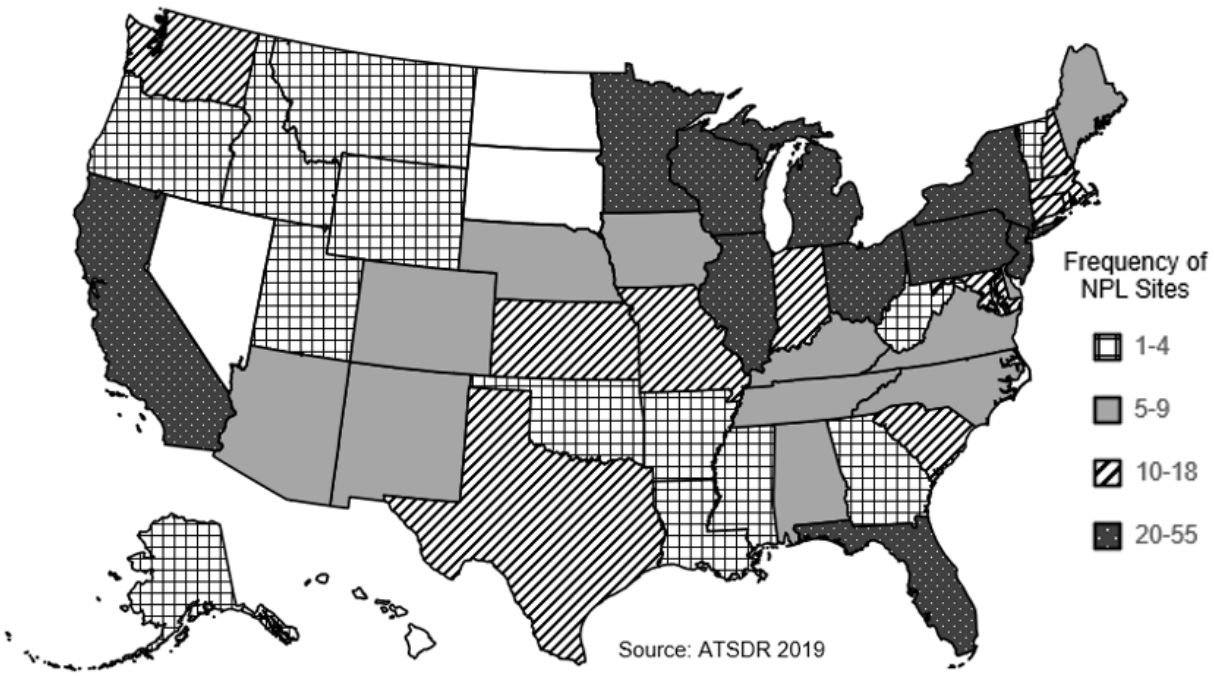
Property	Information	Reference
Molecular weight	96.94	EPA 2017a
Color	Colorless	Larranaga et al. 2016
Physical state	Liquid	Haynes 2014
Melting point	-122.5°C	Haynes 2014
Boiling point	31.7°C at 760 mmHg	O'Neil et al. 2013
Density at 20°C	1.213 g/cm^3	Haynes 2014
Odor	Mild sweet odor resembling that of chloroform	O'Neil et al. 2013
Odor threshold:		
Air	2,000–5,000 mg/m^3	EPA 1987
Solubility:		
Water at 25°C	2,420 mg/L	Horvath et al. 1999
Organic solvents	Soluble in organic solvents	O'Neil et al. 2013
Partition coefficients:		
Log K_{ow}	2.13; 1.32	Hansch et al. 1995; WHO 2003
Log K_{oc}	1.81	Chu and Chan 2000; Sabljic et al; 1995
Vapor pressure at 25°C	600 mm Hg	Boublik et al. 1984
Henry's law constant at 20–25°C	2.61x10^{-2} atm-m^3/mol	Gossett 1987
Autoignition temperature	457°C	Larranaga et al. 2016
Flashpoint	-10°C (open-cup) -19°C (closed-cup)	EPA 1985; Larranaga et al. 2016
Conversion factors	1 ppm=3.97 mg/m^3 1 mg/m^3=0.25 ppm	Verschueren 1983 Verschueren 1983
Explosive limits	5.6–11.4% v/v in air	Larranaga et al. 2016

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

1,1-Dichloroethene has been identified in at least 610 of the 1,867 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2019). However, the number of sites in which 1,1-dichloroethene has been evaluated is not known. The number of sites in each state is shown in Figure 5-1. Of these sites, 608 are located within the United States, and 2 are located in Puerto Rico (not shown).

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



- The potential for human exposure to 1,1-dichloroethene is greatest for individuals at its point of production, formulation, or transport. Occupational exposure to 1,1-dichloroethene may occur by inhalation and dermal contact. Workers involved in cleaning up hazardous waste or spill sites that contain 1,1-dichloroethene may potentially be exposed to this chemical.

- The general population may be exposed to 1,1-dichloroethene by inhalation of ambient air and ingestion of drinking water contaminated with this chemical. Those who live near hazardous waste sites contaminated with 1,1-dichloroethene, especially those who receive their drinking water from underground sources, may potentially be exposed to 1,1-dichloroethene, the levels of which will vary by location. Quantitative data that address levels of human exposure to 1,1-dichloroethene are limited.

- 1,1-Dichloroethene has been detected in air, surface water, groundwater, and soil, with the frequency of detection and the concentrations greatest near source areas (e.g., industrial areas, landfills, hazardous wastes sites).

- The primary sources of 1,1-dichloroethene in the environment are related to its synthesis, fabrication, and transport, and the manufacture of its polymer products. Smaller amounts of 1,1-dichloroethene may be released to surface water and soil primarily due to waste disposals. Most 1,1-dichloroethene in the environment evaporates quickly and enters the air. 1,1-Dichloroethene can enter soil, water, and air in large amounts during an accidental spill. It can also enter the environment as a degradation product of other chemicals in the environment.

- In the air, 1,1-dichloroethene undergoes rapid degradation with photochemically-produced hydroxyl radicals. 1,1-Dichloroethene has calculated atmospheric half-lives of 2–3 days. 1,1-Dichloroethene breaks down very slowly in water and the majority of this chemical will evaporate into air. 1,1-Dichloroethene is not readily transferred to fish or birds, and only very small amounts enter the food chain. In soil, 1,1-dichloroethene either evaporates to the air or percolates down through soil with rainwater and enters groundwater. Small living organisms in soil and groundwater may transform it into other less harmful substances, although this is a slow process.

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

1,1-Dichloroethene is an anthropogenic compound and does not occur naturally, although it is found in landfills as the result of the breakdown of polyvinylidene chloride products and as a degradation product of other chemicals in the environment (EPA 1985; Zhang et al. 2006). 1,1-Dichloroethene is produced commercially by the dehydrochlorination of 1,1,2-trichloroethane with excess lime or caustic or by thermal decomposition of 1,1,1-trichloroethane (O'Neil et al. 2013; WHO 2003). 1,1-Dichloroethene can readily polymerize at room temperature following addition of peroxides and polymerizes after the addition of initiators via ionic or free radial reactions (Grayson 1985; Larranaga et al. 2016). Commercial products usually contain small portions of an inhibitor to prevent its polymerization reaction. Several inhibitors have been invented for this purpose; for example, p-hydroxyanisole (CAS Registry Number: 150-76-5; synonym: MEHQ), which can be added (typically at 200 ppm) and removed by distillation or washing (Grayson 1985; O'Neil et al. 2013). Typically, a commercial-grade product contains 99.8% 1,1-dichloroethene (EPA 1985).

1,1-Dichloroethene is manufactured in chemical plants located in Texas and Louisiana. Two producers listed in the United States are Dow Chemical and Pittsburgh Paint and Glass (PPG) Industries (SRI 2011). In 1978, plant capacity at PPG Industries was estimated at 78 million pounds/year (EPA 1985).

Production capacity in 1985 was reported as 178 million pounds/year (EPA 1985). This decreased from 1977, when production capacity was estimated at 270 million pounds (EPA 1977b). Up-to-date data for the United States can be found using the Chemical Data Reporting (CDR) website, which reports information on the production and use of chemicals manufactured, imported, and exported. The CDR (EPA 2020) lists two domestic manufacturers of 1,1-dichloroethene for 2016, Owensboro Specialty Polymers Inc. in Owensboro, Kentucky, using 1,1-dichloroethene as a reactant in the manufacture of adhesives and sealant chemicals, production volume of 9,088,728 pounds; and Olin Corporation's plant in Freeport, Texas, using 1,1-dichloroethene as a reactant in the manufacture of plastic material and resins, production volume withheld. The CDR lists two companies for 2012: The Dow Chemical Company's site in Freeport, Texas (manufacturing information is listed as confidential business information [CBI]) and Shin Etsu's Shintech Plaquemine Plant in Plaquemine, Louisiana, with a total production volume of approximately 108,000 pounds in 2011 and 63,000 pounds in 2010 (EPA 2014a). National aggregate production volumes since 2011 have been withheld.

According to the Toxics Release Inventory (TRI), 22 facilities manufactured or processed 1,1-dichloroethene in 2015 (TRI18 2020). These data are listed in Table 5-1. The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

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

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
GA	1	100,000	999,999	6
KY	3	100	999,999	1, 3, 6
LA	6	100	99,999	1, 4, 5, 13, 14
MI	2	100,000	9,999,999	1, 5, 6, 12
NC	1	100,000	999,999	6
NY	1	0	99	12
OH	2	1,000	99,999	12

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

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
TX	5	100	9,999,999	1, 4, 5, 6, 12, 13, 14
WI	1	Not reported	Not reported	Not reported

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

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

Source: TRI18 2020 (Data are from 2018)

5.2.2 Import/Export

No data are available on the import activities for 1,1-dichloroethene. The CDR reported export data for Shin Etsu's Shintech Plaquemine Plant in Plaquemine, Louisiana as slightly over 8,000 pounds for 2011.

5.2.3 Use

1,1-Dichloroethene is used as a reactant for organic chemical synthesis, in the production of polyvinylidene chloride copolymers, and sparingly as a chlorinated solvent (CDR 2018; Larranaga et al. 2016; O'Neil et al. 2013). Because of the instability of the polymer, 1,1-dichloroethene is usually used as a copolymer with acrylonitrile, vinyl chloride, methacrylonitrile, and methacrylate (Grayson 1985; Rossberg et al. 1986). 1,1-Dichloroethene can be copolymerized with vinyl chloride or acrylonitrile to produce flexible films for food packaging, the major applications of polyvinylidene chloride copolymers (EPA 1977b; Larranaga et al. 2016). These polymers, which have been commercially important since their introduction in the early 1940s, are used extensively in many types of flexible packing materials (including barrier, multilayer, and monolayer), as flame retardant coatings for fiber and carpet backing, and in piping, coating for steel pipes, and adhesive applications (EPA 1977b). 1,1-Dichloroethene is found in many food and other packaging materials. Plastic packaging films can contain no more than 10 ppm 1,1-dichloroethene (FDA 1988). If 1,1-dichloroethene is employed as an unavoidable solvent in the production of pharmaceuticals, the U.S. Food and Drug Administration (FDA) has set a concentration limit of 8 ppm in the final product (FDA 2020a).

5.2.4 Disposal

1,1-Dichloroethene is classified as an extremely flammable and toxic liquid (EPA 2009a; WHO 2018; Weiss 1986). The EPA (1987) requires compliance with the regulations of the Resource Conservation and Recovery Act (RCRA) when producing, treating, transporting, storing, or disposing of this substance. RCRA Hazardous Waste Code for 1,1-dichloroethene is U078; its maximum concentration in solid hazardous waste is 0.7 mg/L, above which the solid waste is considered toxic waste and should be disposed of according to the appropriate regulations (EPA 2009a; 2017a). Disposal regulations of 1,1-dichloroethene require dissolving it in combustible solvents and scatter spraying the solvent into a furnace with an afterburner and alkaline scrubber. The waste mother liquor likely contains higher concentrations (>200 ppm) of the inhibitor, MEHQ. Disposal of accidental spills should be according to local regulations; collect leaking and spilled liquid in sealable containers and absorb remaining liquid in sand or an inert absorbent (WHO 2018).

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 22,653 pounds (~10.28 metric tons) of 1,1-dichloroethene to the atmosphere from 22 domestic manufacturing and processing facilities in 2018, accounted for 99.9% of the estimated total environmental releases from facilities required to report to the TRI (TRI18 2020). These releases are summarized in Table 5-2.

Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use 1,1-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
GA	1	320	0	0	0	0	320	0	320
KY	3	6,111	0	0	0	1	6,111	1	6,112
LA	6	10,740	0	0	0	0	10,740	0	10,740
MI	2	970	25	0	1	0	995	1	996
NC	1	2	0	0	0	0	2	0	2
NY	1	0	0	0	0	0	0	0	0
OH	2	1	0	0	0	0	1	0	1
TX	5	4,510	0	0	0	0	4,510	0	4,510
WI	1	No data	No data	No data	No data	No data	No data	No data	No data
Total	22	22,653	25	0	1	1	22,679	2	22,681

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

RF = reporting facilities; UI = underground injection

Source: TRI18 2020 (Data are from 2018)

Air releases are the largest source of 1,1-dichloroethene releases to the environment, and emissions from polymer synthesis and fabrication industries contribute most to overall atmospheric loading. Singh et al. (1981) have estimated that air emissions of 1,1-dichloroethene from polymer synthesis in the United States range between 2 and 5% of the annual production. EPA (1985) estimated total annual air emissions of 1,1-dichloroethene of ≈650 tons/year, which was 0.8% of the production volume for that year. Over one-half of that total (355 tons) was from the polymer production/fabrication industries. The remaining emissions were from monomer synthesis (223 tons/year; 34%) and monomer storage, handling, and transportation (73 tons/year; 11%). Small amounts of 1,1-dichloroethene (not quantified) were estimated to be released during the incineration (disposal) of polymer products containing the 1,1-dichloroethene monomer, 1,1,1-trichloroethane, and other chlorinated solvents (Oki et al. 1990; Yasuhara and Morita 1988). Crume (1991) reported that 1,1-dichloroethene can be released to the atmosphere by air stripping contaminated groundwater. This process transfers groundwater contaminants into the gaseous phase and subsequently releases them into the atmosphere with no further treatment (the releases were not quantified). However, more recent data indicate that both the number of emission point sources and the total amount of 1,1-dichloroethene released to the atmosphere are much less than EPA's earlier estimates. This decrease is the result of shifts away from the use of the compound by processors and improvements in control technology.

Hazardous waste sites and landfills where 1,1-dichloroethene have been improperly disposed of are additional potential sources of release of the chemical to the atmosphere because of volatilization (see Section 5.4.1).

5.3.2 Water

Estimated releases of 25 pounds (~0.01 metric tons) of 1,1-dichloroethene to surface water from 22 domestic manufacturing and processing facilities in 2018, accounted for 0.11% of the estimated total environmental releases from facilities required to report to the TRI (TRI18 2020). These releases are summarized in Table 5-2.

Industrial releases of 1,1-dichloroethene to surface water contribute to the overall environmental loading of the chemical, but to a much lesser extent than atmospheric emissions. Liquid effluents produced during polymerization operations were estimated to contribute ≈2 tons of waste 1,1-dichloroethene each year (EPA 1977b). Other potential industrial sources of waste 1,1-dichloroethene in surface water are metal finishing and nonferrous metals manufacturing industries, soap and detergent manufacturers,

electric coil coating and battery manufacturers, coal mines, laundries, and industries involving paint and ink formulation. 1,1-Dichloroethene has been measured in raw wastewater from these industries at mean concentrations of 3–760 µg/L (EPA 1981).

Hazardous waste sites where 1,1-dichloroethene has been improperly disposed are additional potential sources of the chemical, although there are no quantitative data available to address how much 1,1-dichloroethene enters the environment from this source. In addition, surface water or groundwater contaminated with 1,1,1-trichloroethane, tetrachloroethylene, 1,1,2-trichloroethylene, and 1,2-dichloroethane can be an additional source of 1,1-dichloroethene through biotic or abiotic elimination or dehydrochlorination transformations (Baek et al. 1990; Cline and Viste 1985; Lesage et al. 1990). Hydrolysis of 1,1,1-trichloroethane in water or water/sediment systems will result in the formation of 1,1-dichloroethene, although it is a very slow process, with a half-life of 350 days at 25°C (Haag and Mill 1988). Total releases of 1,1-dichloroethene from these sources have not been quantified or estimated.

Surface water was analyzed after 39,000 tons of coal ash from an industrial steam station was spilled into the Dan River in Eden, North Carolina on February 2, 2014 (EPA 2017c). Surface water samples taken from the intake waters and river waters between the Danville Water Treatment Plant and South Boston Water Treatment Plant on February 6th, 7th, and 11th 2014 did not contain concentrations of 1,1-dichloroethene above the detection limit of 0.5 µg/L (EPA 2014b, 2014c, 2014d).

5.3.3 Soil

Estimated releases of 1 pound (~0.0004 metric tons) of 1,1-dichloroethene to soils from 22 domestic manufacturing and processing facilities in 2018, accounted for 0.004% of the estimated total environmental releases from facilities required to report to the TRI (TRI18 2020). These releases are summarized in Table 5-2.

Limited information is available on the releases of 1,1-dichloroethene to soil. An estimated total of 180 pounds/year of 1,1-dichloroethene are disposed of in municipal landfills as residual monomer in some consumer products on a national basis (EPA 1977b). Under certain conditions, 1,1-dichloroethene may be released into the environment as a degradation product of other chemicals such as the hydrolysis of 1,1,1-trichloroethane and the dechlorination of trichloroethene under anaerobic conditions (Haag Mill 1988; McNab and Narasimhan 1994; USGS 2006; Zhang et al. 2006).

5.4 ENVIRONMENTAL FATE

5.4.1 Transport and Partitioning

The tendency of a chemical to partition between soil, water, sediment, air, and biota can be inferred from its physical/chemical properties. Based on a vapor pressure of 600 mm Hg (Boublik et al. 1984), most of the 1,1-dichloroethene released into the environment will ultimately partition into the atmospheric compartment as shown by the vapor partitioning model of Mackay and Paterson (1981), although other factors such as water solubility may affect the rate at which the partitioning will occur. In localized situations, intervening processes such as biotransformation, may alter this outcome.

Air. Based on its high vapor pressure, 1,1-dichloroethene will exist entirely in the vapor phase in the ambient atmosphere. Studies on atmospheric removal processes indicate that once in the atmosphere, 1,1-dichloroethene is unlikely to be removed by physical processes such as wet deposition (e.g., rain) or by adsorption to atmospheric particulates (EPA 1980a). An atmospheric residence time of 2.9 days (EPA 1980a) suggests that the potential for limited atmospheric transport from point sources may be possible.

Water. The dominant removal process for 1,1-dichloroethene from surface waters is expected to be volatilization. As the magnitude of the Henry's law constant for 1,1-dichloroethene, 2.61×10^{-2} atm-m^3/mole at 24°C (Gossett 1987) indicates, 1,1-dichloroethene is likely to volatilize rapidly into the atmosphere from water. Because of this, 1,1-dichloroethene is generally not found in surface water in high concentrations. Based on its Henry's Law constant, the volatilization half-life in a model lake 1 m deep with a 0.05 m/second current and a 0.5 m/second wind is estimated to be 3.9 days; the volatilization half-life of 1,1-dichloroethene in a model river 1 m deep flowing 1 m/second with a wind speed of 3 m/second is estimated to be 1 hour (EPA 2012).

Sediment and Soil. 1,1-Dichloroethene spilled onto surface soil will also tend to partition to the atmosphere, while some of the chemical may percolate into the subsurface soil. Once in the subsurface soil, 1,1-dichloroethene will partition between soil and water. 1,1-Dichloroethene has relatively high water solubility and a small log soil organic carbon sorption coefficient (K_{oc}) value of 1.81 (EPA 1982), indicating that 1,1-dichloroethene has high mobility and will migrate through soil without significant retardation by adsorption to organic carbon. Similarly, 1,1-dichloroethene will migrate relatively freely within groundwater.

Other Media. 1,1-Dichloroethene in surface water is unlikely to partition significantly into aquatic organisms. Partitioning of 1,1-dichloroethene from water into aquatic organisms can be predicted in part by the magnitude of the octanol/water partition coefficient (K_{ow}) value. Chemicals with a log K_{ow} of <4.0 are unlikely to bioaccumulate to hazardous levels in human food chains (Veith et al. 1985). The log K_{ow} is 2.13 (Veith et al. 1985) and based upon this calculation, bioaccumulation in the human food chain is not expected to be significant for this compound. An experimental bioconcentration factor (BCF) of 3.1–4.9 L/kg at 0.5 mg/L and ≤13 at 0.5 mg/L measured in carp indicates that the potential for bioconcentration in aquatic organisms is low (CITI 1992).

5.4.2 Transformation and Degradation

Transformations of 1,1-dichloroethene can occur from the reaction with radical species in the atmosphere and from biodegradation under anaerobic conditions in soil or water.

Air. Atmospheric degradation of 1,1-dichloroethene is expected to be dominated by gas-phase oxidation with photochemically produced hydroxyl radicals. An experimental rate constant for this process of 1.09×10^{-11} cm^3/molecule-second at 25°C has been determined (Kwok and Atkinson 1995). Based on a 12-hour day of sunlight, using an average atmospheric hydroxyl radical concentration of 5×10^5 molecule/cm^3, a half-life of 1.5 days can be calculated for this process. A higher atmospheric concentration of hydroxyl radicals (5×10^6 molecules/cm^3) will reduce the half-life of 1,1-dichloroethene from 1.5 days to 3.5 hours (Grosjean 1990). The products expected from this reaction are phosgene, formaldehyde, and chloroacetyl chloride (Tuazon et al. 1988). Pearson and McConnell (1975) reported a tropospheric half-life for 1,1-dichloroethene of 8 weeks, resulting from an experiment with limitations such as non-ideal air characteristics and ±50% reproducibility due to climate parameters noted.

Atmospheric degradation of 1,1-dichloroethene may also occur by a gas-phase reaction with other atmospheric oxidants, namely ozone and nitrate radicals, although these processes are slower than the reaction of 1,1-dichloroethene with hydroxyl radicals (Grosjean 1990). An experimental rate constant for the gas-phase reaction of ozone with 1,1-dichloroethene of 3.7×10^{-21} cm^3/molecule-second at 25°C (Atkinson and Carter 1984) translates to an atmospheric half-life of >8 years for this process using an average atmospheric ozone concentration of 7×10^{11} molecule/cm^3. Nitrate radicals are destroyed by sunlight, and the oxidation of organic compounds by this oxidant is only important at night. The rate constant for the oxidation of 1,1-dichloroethene by nitrate radicals, 1.78×10^{-15} cm^3/molecule-second at 25°C (Sabljic and Gusten 1990), translates to a half-life of 19 days in a moderately polluted atmosphere,

although at nitrate concentrations of 50 ppt the half-life may be reduced to 6 days (Grosjean 1990). Using Fourier transform infrared spectroscopy (FTIR) spectrometry, 1,1-dichloroethene reaction with hydroxyl radicals and nitrates was observed; reaction products of 1,1-dichloroethene with hydroxyl radicals and nitrates in air include chloroacetyl chloride, phosgene, formaldehyde, carbon monoxide, and nitric acid; a hydroxyl radical reaction rate constant of $12x10^{-12}$ cm^3/molecule-second was calculated corresponding to an atmospheric half-life of approximately 16 hours (EPA 1983). Lacking chromophores that absorb radiation at wavelengths >290 nm, direct vapor phase photolysis is not expected to be an important fate process for 1,1-dichloroethene (Lyman et al. 1990).

Water. Photolysis and hydrolysis of 1,1-dichloroethene in natural aquatic media are not significant environmental fate processes (EPA 1982). The estimated half-life for the hydrolysis of 1,1-dichloroethene at 25°C under neutral (or slightly basic) conditions is $1.2x10^8$ years (Jeffers et al. 1989). Estimated hydrolysis half-lives of 6–9 months at pH values ranging from 4.5 to 8.5 have also been reported (Cline and Delfino 1987). Conflicting results have been obtained for the aerobic biotransformation of 1,1-dichloroethene. Biotransformation under anaerobic conditions is likely the dominant transformation process for 1,1-dichloroethene in groundwater; however, complete mineralization has not been confirmed. 1,1-Dichloroethene and its transformation products have been postulated as toxic to microbial populations. Transformation capacities were measured for chlorinated hydrocarbons using two mixed and two pure methane-oxidizing cultures; 1,1-dichloroethene exhibited the greatest toxicity with mean transformation values of 0.11, 0.25, 0.39, and 0.36 μmol/mg being an order of magnitude lower than other similar chlorinated hydrocarbons (Chang and Alvarez 1996). Oxidation of 1,1-dichloroethene by methane and aromatic monooxygenases has been demonstrated with removal rates greater than 95% in 24 hours (Chauhan et al. 1998; Dolan and McCarty 1995). In aqueous batch studies at 20°C using aquifer material from a Superfund site under aerobic conditions, 1,1-dichloroethene was not found to be toxic at concentrations up to 1 mg/L, yet its transformation products were highly toxic; biotransformation of 1,1-dichloroethene as a result of methyl monooxygenase activity was apparent, but ceased after the first few hours of incubation with the mixed methanotrophic culture in the presence and absence of formate with transformation rates of 0.063 and 0.045 μmol 1,1-dichloroethene/mg of total suspended solids, respectively (Dolan and McCarty 1995). Pearson and McConnell (1975) found no evidence for biotransformation of 1,1-dichloroethene under aerobic conditions in water. Additionally, 0% biodegradation was observed after 28 days in an aerobic closed bottle test using an activated sludge inoculum (OECD 301D) (CITI 1992). In contrast, aerobic degradation may occur under certain conditions; Tabak et al. (1981) reported transformation of 54% of 5 mg/L and 30% of 10 mg/L test concentrations of 1,1-dichloroethene under aerobic conditions within 1 week after incubation with a

domestic waste water seed; these removal figures were adjusted to account for volatilization losses from control flasks of 24% for the 5 mg/L and 15% for the 10 mg/L test concentrations. Under anaerobic conditions, Ensign et al. (1992) observed that 1,1-dichloroethene was not degraded efficiently by propylene-grown *Xanthobacter* cells (strain Py2); the environmental media was not reported. However, Wilson et al. (1986) studied the behavior of 1,1-dichloroethene in authentic aquifer material known to support methanogenesis. The disappearance of 1,1-dichloroethene was observed with an initial 16-day lag phase and vinyl chloride, the major degradation product, was found in trace amounts. Baek et al. (1990) observed the biodegradation and formation of vinyl chloride under anaerobic conditions when 1,1-dichloroethene was incubated with digested sludge under both fermentative and methanogenic conditions. In an anaerobic continuous-flow column study evaluating the reductive dechlorination of perchloroethylene, reduction of 1,1-dichloroethene also led to vinyl chloride (Vogel and McCarty 1985).

Sediment and Soil. In studies simulating anaerobic conditions in groundwater and landfills, vinyl chloride was produced from the reductive dechlorination of 1,1-dichloroethene by microorganisms in anoxic sediment microcosms after 1–3 weeks of incubation (Barrio-Lage et al. 1986; Hallen et al. 1986); reported first-order rate constants for the depletion of 1,1-dichloroethene in anoxic sediments were $3.57x10^{-4}$ and $1.67x10^{-4}$ $hours^{-1}$ corresponding to half-lives of 81 and 173 days, respectively (Barrio-Lage et al. 1986). A methane-utilizing culture isolated from lake sediment degraded 600 ng/mL 1,1-dichloroethene to 200 ng/mL under aerobic conditions within 2 days; the degradation products were nonvolatile and did not include vinyl chloride, which is known to be formed under anaerobic conditions (Fogel et al. 1986). Under aerobic conditions in soil microcosms with aquifer material, no measurable biotransformation of 1,1-dichloroethene was observed and any loss was attributed to sorption (Dolan and McCarty 1995).

5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to 1,1-dichloroethene depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of 1,1-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 1,1-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 lowest limit of detections that are achieved by analytical analysis of environmental media. An overview summary of the range of concentrations detected in environmental media is presented in Table 5-4.

Table 5-3. Lowest Limit of Detection Based on Standards

Media	Detection limit	Reference
Air	7 µg/sample	Foerst 1979; NIOSH 1994
Drinking water	<0.2 µg/L	Eichelberger et al. 1990
Surface water and groundwater	0.13–2.8 µg/L	EPA 1984a, 1984c, 1986b
Soil/chemical waste	10 ppm	Deleon et al. 1980
Sediment/solids sludges/wastes	Soil, sediment, 5 µg/L; wastes 0.5 mg/kg	EPA 1986c
Whole blood	3.1 ppt	Ashley et al. 1992
Human tissue (adipose, kidney, liver brain)	~50 pg	Lin et al. 1982
Alveolar air/breath	<5–1 µg/m^3	Pellizzari et al. 1985; Raymer et al. 1990; Wallace et al. 1984
Fish tissue	10 µg/kg	Easley et al. 1981
Food	<0.005 ppm	Gilbert et al. 1980

Table 5-4. Summary of Environmental Levels of 1,1-Dichloroethene

Media	Low	High	Reference
Surface water (ppb)	<0.14	48,000	USGS 2006
Groundwater (ppb)	<0.13	<16	USGS 2006

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

Table 5-5. 1,1-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
Water (ppb)	24	33.8	15.0	484	257
Soil (ppb)	360	279	34.8	79	57

Table 5-5. 1,1-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
Air (ppbv)	1.31	4.42	45.5	39	30

[a]Concentrations found in ATSDR site documents from 1981 to 2017 for 1,854 NPL sites (ATSDR 2019). 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

Air monitoring data for 1,1-dichloroethene have been compiled in Table 5-6.

The EPA TEAM (Total Exposure Assessment Measurement) studies measured 1,1-dichloroethene concentrations in 1,085 personal air samples collected from 350 New Jersey residents (discrepancy in the actual number of residents sampled) over three seasons. Only 77 (7%) of the samples had measurable concentrations of 1,1-dichloroethene, and 107 (10%) of the samples had trace levels. The detection limit ranged from 3 to 14 μg/m^3 (Wallace 1991). Headspace analysis of air emissions from eight different household bleach products during use detected 1,1-dichloroethene concentrations of 1.1–1,500 μg/m^3; it was suggested that sodium hypochlorite (NaOCl) in the bleach may react to generate halogenated VOCs (Odabasi 2008).

About 50% of 1,1-dichloroethene volatilizes from water while showering. Volatility from other household uses of water ranges from about 20% (sinks, toilets) to 70% (dishwashers). Thus, there is potential for inhalation exposure during showering, bathing, and other household water uses, such as dishwashers, clothes washers, toilets, and sinks. ATSDR's three-compartment Shower and Household Water-Use Exposure (SHOWER) model predicts air concentrations in the shower stall, bathroom, and main house throughout the day for households with up to eight members. Using concentrations in water and human activity patterns, the model estimates a daily TWA exposure concentration from breathing indoor air. The model also estimates dermal doses from skin contact while bathing and washing hands. The model is a desktop application that is available by sending a request to showermodel@cdc.gov.

Table 5-6. Air Monitoring Data for 1,1-Dichloroethene

Location(s)	Geographic type	Date(s)	Range	Mean concentration	Notes	Reference
Palermo Wellfield Superfund Site, Washington	Ambient air monitoring sites	July 2019; September 2018; March and December 2017; May 2016; September 2015	0.12–0.16 µg/m^3	Not detected: material analyzed for, but not detected above the method LOD	Detection/quantitation limits of the methods used: 0.12, 0.13, and 0.16 µg/m^3; multiple samples collected at Superfund site	WQP 2020
Pennsylvania, Texas, Rhode Island, Ohio, Kentucky, Arizona Colorado, Florida Georgia, Illinois, Indiana, Massachusetts, Michigan, Missouri, New Jersey, New York, North Carolina, Oklahoma, Utah Vermont, Virginia, Washington	Ambient air monitoring sites	2017		0.059 ppbv	Detected in 11 out 124 samples; Philadelphia, Pennsylvania; Deer Park, Texas; Pawtucket, Rhode Island; Cincinnati, Ohio; Calvert, Kentucky, Laredo, Texas; Denton, Texas; Dallas, Texas	EPA 2017b
Arizona, Colorado, Florida, Georgia, Illinois, Indiana, Iowa, Kentucky, Massachusetts, Michigan, Missouri, New Jersey, New York, North Carolina, Ohio, Oklahoma, Pennsylvania, Rhode Island, Texas, Utah, Virginia, Washington	Ambient air monitoring sites	2016		0.0013–0.056 ppbv	Detected in 12 out 124 samples; Pawtucket, Rhode Island; Deer Park, Texas; Candor, North Carolina; Philadelphia, Pennsylvania; Raleigh, North Carolina; Davie, Florida; Fort Lauderdale, Florida; Coconut Creek, Florida; Dania, Florida	EPA 2016a
New Jersey	Ambient air	1983–1984	Maximum: 97 ppb	0.39–38.9 ppb, measured at waste sites, and an arithmetic mean concentration of 2.6 ppb measured at the sanitary landfill		Harkov et al. 1985; LaRegina et al. 1986

Table 5-6. Air Monitoring Data for 1,1-Dichloroethene

Location(s)	Geographic type	Date(s)	Range	Mean concentration	Notes	Reference
New Jersey	Ambient air	July–August 1981		0.35–0.38 ppb	Newark, Elizabeth, and Camden New Jersey	Harkov et al. 1987
Kanawha Valley, West Virginia; Los Angeles, California; and Houston, Texas	Ambient air	1986–1987		0.84 ppb	Detected in 24 of 79 ambient air samples	Pleil et al. 1988
U.S. cities	Ambient air	Prior to 1981	0.005–0.03 ppb			Singh et al. 1981, 1982
Research Triangle Park, North Carolina	Indoor air	Prior to 1985		47.3 ppb (summer); 7.1 ppb (winter)	26 homes and apartments	EPA 1985
United States	Ambient and indoor air	1988		4.6 ppb	Daily average concentration from rural, suburban, urban, and source-dominated sites	EPA 1988a
United States	Ambient and indoor air	1988	Median 0.0 ppbv (ambient and indoor)	4.612 ppbv ambient; 19.665 ppbv indoor	Daily average ambient concentration from rural, suburban, urban, and source-dominated sites (1,275 data points); daily average indoor concentration from residential, offices, and personal (2,120 data points)	EPA 1988a
Palermo Wellfield Superfund Site, Washington	Indoor air	April and October 2013; February 2014	0.16–0.17 µg/m^3	Not detected: the analyte was analyzed for, but was not detected, at a level greater than or equal to the level of the adjusted contract required quantitation limit for sample and method	Detection/quantitation limits of the methods used: 0.16 and 0.17 µg/m^3	WQP 2020

LOD = limit of detection

Based on vapor pressure and Henry's law constant, 1,1-dichloroethene has the potential to be a contaminant of concern for vapor intrusion into homes or other buildings (ATSDR 2016; EPA 2015). A review of vapor intrusion data from 148 ATSDR public health assessments completed between 1994 and 2010 identified 31 sites with detected concentrations of 1,1-dichloroethene in groundwater, soil gas, or air (Burk and Zarus 2013). 1,1-Dichloroethene was detected in indoor air at 9 of the 31 vapor intrusion sites. Two of the sites had measured indoor air concentrations greater than ATSDR's MRL: the Chemical Commodities Incorporated site from Olathe, Kansas (ATSDR 2003) had a measured indoor air concentration of 4.4 μg/m^3, and the Valmont Trichloroethylene site from West Hazelton, Pennsylvania (ATSDR 2006) had a measured indoor air concentration of 7.5 μg/m^3. All of the concentrations measured were less than the BMCL used as the basis of the inhalation MRL and were not expected to be of concern for health effects.

5.5.2 Water

Water monitoring data for 1,1-dichloroethene have been compiled in Table 5-7.

1,1-Dichloroethene has been detected infrequently at low concentrations in urban runoff that will contribute to surface water concentrations. (Cole et al. 1984). 1,1-Dichloroethene has been detected in 25.2% of 178 contaminated sites monitored under the Comprehensive Emergency Response, Compensation, and Liability Act (CERCLA), making it the fifth most frequently detected organic contaminant at these sites (Plumb 1987). Contamination of groundwater at an industrial site in Waite Park, Minnesota, resulting from the mishandling of waste product, paint, and solvent led to a maximum 1,1-dichloroethene concentration of 88 μg/L in deep monitoring wells and 22 μg/L in shallow wells (ATSDR 1990). This aquifer contamination led to a maximum 1,1-dichloroethene concentration of 94 μg/L in Waite Park municipal wells, resulting in this city's water supply being listed as an NPL site. The disposal of organic chemicals in trenches at a waste disposal site near Ottawa, Canada, resulted in 1,1-dichloroethene groundwater concentrations ranging from 0.9 to 60 μg/L in 43% of samples taken from a 37-well monitoring network in 1988 (Lesage et al. 1990). Leachate originating from the Orange County and Alachua Municipal Landfills in north central Florida resulted in groundwater contamination near the landfills. The average concentrations of 1,1-dichloroethene in wells sampled near the Orange County Landfill and the Alachua Municipal Landfill were 0.12 and <1.0 μg/L, respectively (Hallbourg et al. 1992).

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

Location(s)	Geographic type	Date(s)	Range	Mean concentration	Notes	Reference
Grenada, Mississippi	Industrial-related site	January 2016	Not detected		Not detected at or above the detection limit of 0.50 ppb (0.5 µg/L)	Grenada 2016b
Arizona; Delaware; Minnesota; New Mexico; Oregon; Pennsylvania; Tennessee; Texas; Virginia; Washington	Surface water	2019	Not detected		Material analyzed for, but not detected above the lower reporting limit of 0.1–1.0 µg/L	WQP 2020
Arizona; Nevada; New Jersey; New Mexico; Pennsylvania; North Carolina; Oregon; Tennessee; Texas; Virginia; Washington	Surface water	2018	Not detected		Material analyzed for, but not detected above the lower reporting limit of 0.1–1.0 µg/L	WQP 2020
Arizona; California; New Jersey; New Mexico; New York; North Carolina; Oregon; Tennessee; Texas; Virginia; Washington	Surface water	2017	Not detected		Material analyzed for, but not detected above the Lower Reporting Limit of 0.1–1.0 µg/L	WQP 2020
USGS New Mexico Water Science Center	Groundwater	January 2020	Not detected		Material analyzed for, but not detected above the lower reporting limit of 0.6 µg/L	WQP 2020
Arizona Department of Environmental Quality; Boomsnub/Airco Superfund Site EPA Region 10; Northern Ute Indian Tribe (UT); Palermo Wellfield Superfund Site, Washington; State of Oregon Department of Environmental Quality	Groundwater; Superfund sites	2019	Not detected–170 ug/L		Activity depth: 4.13–396 feet; LOD: 0.08–5.0 µg/L	WQP 2020
USGS Water Science Centers of: Alabama; California; Colorado; Florida; Georgia; Idaho; Illinois; Indiana; Kentucky; Maine; Massachusetts; Minnesota; Mississippi; Missouri; Nebraska; New Hampshire; New Jersey; New Mexico; New York; Ohio; Pennsylvania; South Carolina; Tennessee; West Virginia; Wyoming	USGS monitoring sites	2019	Not detected– 2 µg/L		Activity depth: 5–1,414 feet; LOD: 0.1–1.0 µg/L	WQP 2020

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

Location(s)	Geographic type	Date(s)	Range	Mean concentration	Notes	Reference
Arizona Department of Environmental Quality; Boomsnub/Airco Superfund Site EPA Region 10; Minnesota Pollution Control Agency - Ambient Groundwater; Northern Ute Indian Tribe (UT); Palermo Wellfield Superfund Site, Washington; State of Oregon Department of Environmental Quality	Groundwater; Superfund sites	2018	Not detected-9.1 ug/L		Activity depth: 4.13–250 feet; LOD: 0.08–2.0 µg/L	WQP 2020
USGS Water Science Centers of: Arizona; California; Colorado; Georgia; Idaho; Illinois; Kansas; Maryland; Minnesota; Missouri; Montana; Nebraska; New Jersey; New Mexico; New York; North Dakota; Oklahoma; Pennsylvania; South Carolina; Tennessee; Texas; Washington	USGS monitoring sites	2018	Not detected- 16 ug/L		Activity depth: 4.3–1,414 feet; LOD: 0.1–1.0 µg/L	WQP 2020
Arizona Department of Environmental Quality; Blackfeet Nation (Montana); Boomsnub/Airco Superfund Site EPA Region 10; Minnesota Pollution Control Agency - Ambient Groundwater; Northern Ute Indian Tribe (UT); Palermo Wellfield Superfund Site, Washington; Sokaogon Chippewa Community; State of Oregon Department of Environmental Quality	Groundwater; Superfund Sites	2017	Not detected		Activity depth: 4.13–237.4 feet; LOD: 0.0046–2.0 µg/L	WQP 2020
USGS Water Science Centers of: Arizona; California; Colorado; Connecticut; Georgia; Idaho; Illinois; Iowa; Kansas; Maryland; Massachusetts; Missouri; New Hampshire; New Jersey; New Mexico; New York; Oregon; Pennsylvania; Puerto Rico; Tennessee; Texas; Utah; Wisconsin; Wyoming	USGS monitoring sites	2017	Not detected–13.8 µg/L		Activity depth: 4–1,414 feet; LOD: 0.1–1.0 µg/L	WQP 2020

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

Location(s)	Geographic type	Date(s)	Range	Mean concentration	Notes	Reference
United States	Domestic well water	1985–2002	Not reported	Not reported	Detected in 19 of 1,207 water samples; 1 of 2,400 samples above the EPA MCL	Rowe et al. 2007
South Carolina	Surface water at a VOC-contaminated site	2000–2006	<0.14–48,000 µg/L	Not reported	Solid Waste Management Unit 12, Naval Weapons Station Charleston, North Charleston, South Carolina	USGS 2006
South Carolina	Groundwater at a VOC-contaminated site	2000–2006	<0.13–<16 µg/L	Not reported	Solid Waste Management Unit 12, Naval Weapons Station Charleston, North Charleston, South Carolina	USGS 2006
United States	Domestic well water	2000–2001	Not reported	Not reported	Detected in two wells, one above the EPAs MCL	Aelion and Conte 2004
United States	Groundwater wells	1985–1995	Not reported	Not reported	Detected in 3% of urban wells, and 0.3% of rural wells	Squillace et al. 1999
United States	Domestic well water	1982	Not reported	Median concentration of 0.3 µg/L	Detected in 9 of 466 water samples	Cotruvo 1985
United States		Prior to 1984	Maximum: 6.3 µg/L	Subset median values: 0.28–1.2 µg/L	Detected in 2.3% of 945 samples of finished drinking water taken from community-based groundwater sources in a nationwide survey; quantification limit of 0.2 ppb	Rajagopal and Li 1991; Westrick et al. 1984
United States	Finished water	Prior to 1985	0.2–0.5 µg/L (estimated mean 0.3 µg/L)	Not reported	About 3% of the drinking water supplies in the United States	EPA 1985
United States	Urban storm water runoff	Prior to 1984	1.5–4 µg/L	Not reported	Nationwide Urban Runoff Program (NURP)	Cole et al. 1984

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

Location(s)	Geographic type	Date(s)	Range	Mean concentration	Notes	Reference
U.S. cities	Groundwater	Prior to 1980			Detected in 7.1% of samples	EPA 1980b
U.S. cities	Raw and finished surface water	Prior to 1980	0.2–0.51 µg/L	0.36 µg/L	Not detected in a survey of 105 raw water samples; detected in 1.9% of 103 finished water samples	EPA 1980b
United States		Prior to 1985			Detected in 6% of 8,714 surface water samples monitored nationwide	Staples et al. 1985
United States	Surface waters near industrial sites	Prior to 1977	<1–550 µg/L			Going and Spigarelli 1977c
United States		Prior to 1985			Detected in 3.3% of 1,350 effluent samples monitored nationwide	Staples et al. 1985
United States	Raw and treated waste waters from industrial related site	Prior to 1981	<1,000–>5,000 µg/L		Raw and treated waste waters: from industries involving paint and ink formulation, soap and detergent manufacturing, coil coating, battery manufacturing, coal mining, and laundries (minimum), and from the metal finishing and nonferrous metals manufacturing industries (maximum)	EPA 1981

EPA = U.S. Environmental Protection Agency; LOD = limit of detection; MCL = maximum contaminant level; USGS = U.S. Geological Survey; VOC = volatile organic compound

5.5.3 Sediment and Soil

No information is available on concentrations of 1,1-dichloroethene in surface soil, although this chemical is often found at hazardous waste sites. Because of the tendency of 1,1-dichloroethene to partition into the atmosphere, with remaining material having the potential to percolate into groundwater, ambient concentrations in surface soil are expected to be low.

Data compiled from the Retrieval (STORET) Data Warehouse reports monitoring data from EPA Great Lakes National Program, which includes monitoring of 1,1-dichloroethene. Limited information is reported with no specific concentrations listed; percent recoveries of 68–127% for were reported for 1,1-dichloroethene in 126 sediment samples taken in April, June, and October of 2011 at core depths between 0.15 and 10.3 (WQP 2017).

1,1-Dichloroethene was analyzed for, but was not detected, at a concentrations greater than or equal to the method quantitation/detection limits ranging from 0.096 to 430 mg/kg in monitoring samples of subsurface soil and sediment by the U.S. Geological Survey (USGS) Texas Water Science Center in June and August 2019 (WQP 2020).

5.5.4 Other Media

1,1-Dichloroethene copolymers are used in the manufacture of films used in food packaging. Residual 1,1-dichloroethene monomer has been detected at concentrations of <0.02–1.26 ppm in retail food packaging films containing polyvinylidene chloride; residues in a variety of foodstuffs wrapped with the films were in the range of ≤0.005–0.01 ppm (Gilbert et al. 1980). Concentrations of residual 1,1-dichloroethene in household films used to package food were reported by Birkel et al. (1977) to be 6.5–10.4 ppm (average 8.8 ppm). At one time, some films contained as much as 30 ppm 1,1-dichloroethene (Birkel et al. 1977).

1,1-Dichloroethene was detected in a composite sample of Rigolets clams obtained from Lake Pontchartrain, Louisiana, in 1980 at a concentration of 4.4 ppb wet weight (Ferrario et al. 1985).

5.6 GENERAL POPULATION EXPOSURE

The general population is most likely to be exposed to 1,1-dichloroethene by inhalation of contaminated air and ingestion of food and drinking water contaminated with 1,1-dichloroethene. Exposure potential is expected to be higher near hazardous waste sites containing 1,1-dichloroethene. Occupational exposure to 1,1-dichloroethene is most likely to occur via inhalation and dermal absorption during the production and processing of this chemical.

Information and experimental data on exposure of the general population to 1,1-dichloroethene are limited. An EPA TEAM study conducted from 1980 to 1987 reported that the average exposure of the general population to 1,1-dichloroethene is 6.5 μg/m^3 based on personal air samples from 350 homes in New Jersey (Wallace 1991).

The FDA estimated the cumulative daily intake of 10 polymeric materials produced with 1,1-dichloroethene used in food contact applications at 0.00035 mg/kg body weight/day (FDA 2020b).

The Fourth National Report on Human Exposures to Environmental Chemicals, published and updated by the Centers for Disease Control and Prevention reporting biomonitoring data from the NHANES shows that concentrations of 1,1-dichloroethene in whole blood were below the detection limit of 0.009 ng/mL in samples from 1,364; 3,163; and 2,810 members of the U.S. general population for the survey years 2003–2004, 2005–2006, and 2007–2008, respectively (CDC 2017).

The National Occupational Hazard Survey (NOHS), conducted by the National Institute for Occupational Safety and Health (NIOSH), estimated that 56,857 workers in 3,853 plants were potentially exposed to 1,1-dichloroethene in the workplace in 1970 (NIOSH 1976). These estimates were derived from observation of the actual use of 1,1-dichloroethene (1%), the use of trade-name products known to contain 1,1-dichloroethene (19%), and the use of generic products suspected of containing the compound (80%). The largest numbers of exposed workers were special trade contractors or in the fabricated metal products industry or wholesale trade industry. The occupational groups of exposed workers consisted of carpenters, warehousemen (not otherwise classified), and miscellaneous machine operators.

Data from a second workplace survey, the National Occupational Exposure Survey (NOES), conducted by NIOSH from 1980 to 1983, indicated that 2,679 workers, including 291 women, in 97 plants were potentially exposed to 1,1-dichloroethene in the workplace in 1980 (NIOSH 1984). The greatest number

of exposed workers were chemical technicians. All estimates were derived from observations of the actual use of the compound.

1,1-Dichloroethene was produced in significant amounts that under certain conditions may approach 100%, from the thermal degradation of 1,1,1-trichloroethane (Glisson et al. 1986). This implies that inadvertent exposure to 1,1-dichloroethene may occur in many industrial situations when 1,1,1-trichloroethane is used in the vicinity of operations involving heat, such as welding or soldering and metal cleaning. 1,1-Dichloroethene has also been detected as a pyrolysis product of the pesticide endosulfan in tobacco smoke (Chopra et al. 1978).

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Human exposure to 1,1-dichloroethene is potentially highest in workplace settings and among populations residing in the vicinity of hazardous waste sites where the compound may contaminate environmental media.

The presence of residual monomeric 1,1-dichloroethene in polymeric food wraps and other consumer products is another potential source of human exposure. Exposure from these sources is difficult to estimate. However, there is no evidence in the literature to implicate consumer products as major sources of 1,1-dichloroethene exposure (EPA 1985).

In addition to releases from hazardous waste sites, ambient air and water may be contaminated with 1,1-dichloroethene by releases from industrial production and polymerization processes (EPA 1977, 1985a; Wang et al. 1985a, 1985b). Levels are significantly higher in areas surrounding production sites (EPA 1977b, 1985).

CHAPTER 6. ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 1,1-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 1,1-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.

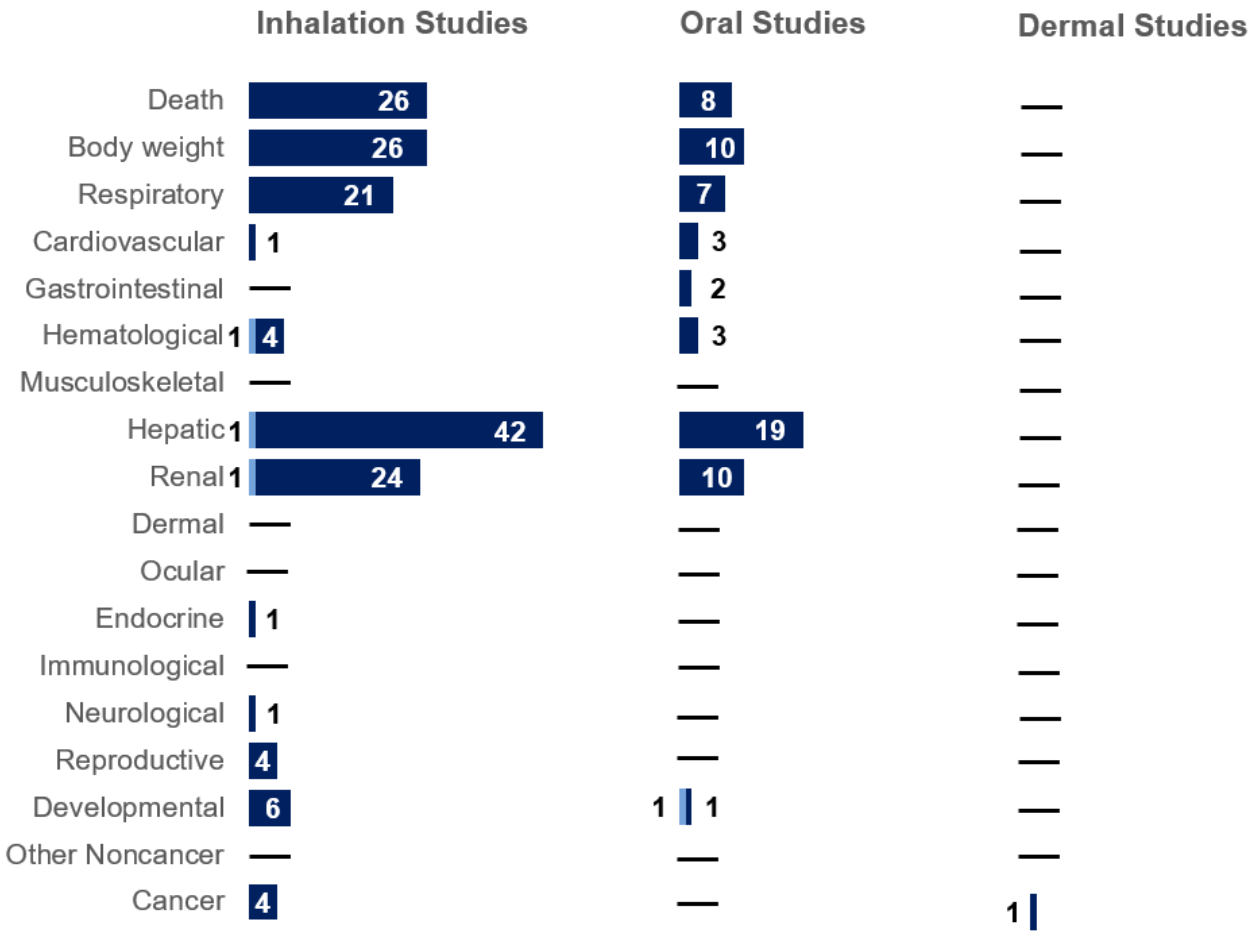
6.1 INFORMATION ON HEALTH EFFECTS

Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to 1,1-dichloroethene that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of 1,1-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.

There is little information available concerning the long-term health effects of 1,1-dichloroethene in humans following inhalation exposure. Most of the information concerning health effects in humans is reported in occupational studies that are difficult to interpret because of limitations in study design (e.g., exposure levels and duration cannot be quantified and concurrent exposure to other toxic substances cannot be ruled out). No information concerning oral or dermal exposure to 1,1-dichloroethene in humans was found in the reviewed literature.

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

Potential hepatic, body weight, renal, and respiratory effects were the most studied endpoints
The majority of the studies examined inhalation exposure in **animals** (versus **humans**)



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

The effects of 1,1-dichloroethene in animals following inhalation and oral exposure have been studied in a variety of species following acute, intermediate, and chronic exposure durations. One oral exposure study reported observations of the "appearance" and "demeanor" of test animals, but this was not considered an appropriate analysis of possible neurological or behavioral effects. Genetic effect endpoints were examined following inhalation exposure only. Carcinogenicity studies in animals following exposure by the oral, inhalation, and dermal routes are available.

6.2 IDENTIFICATION OF DATA NEEDS

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

Acute-Duration MRLs. The available inhalation database was not considered adequate for derivation of an acute-duration inhalation MRL for 1,1-dichloroethene. No exposure-response human data are available. The lowest LOAEL for acute-duration inhalation exposure of laboratory animals is a serious LOAEL of 15 ppm for a study in which death and maternal body weight loss occurred in rats exposed to 1,1-dichloroethene vapor for 22–23 hours/day during GDs 6–16 (EPA 1977a).

The available oral database was not considered adequate for derivation of an acute-duration oral MRL for 1,1-dichloroethene. Some studies did not provide dose-response data because only a single dose level was used. Many of the available studies employed fasted animals which are known to be more sensitive than nonfasted rats to 1,1-dichloroethene-induced adverse effects following oral exposure. Among studies that employed multiple dose levels and nonfasted animals, the lowest LOAEL is 100 mg/kg/day for 11% depressed body weight in female rats administered 1,1-dichloroethene by gavage for 14 days (NTP 1982). Results from inhalation studies and longer-term oral studies identify the kidney as a sensitive target of 1,1-dichloroethene toxicity in mice. However, available acute-duration oral studies in mice do not include dose-response assessment of the kidney. Additional acute-duration inhalation and oral studies are needed to examine exposure-response relationships; such studies should evaluate comprehensive sets of endpoints, including the liver and kidney.

Intermediate-Duration MRLs. The database was considered adequate for derivation of an intermediate-duration inhalation MRL for 1,1-dichloroethene. The database was not considered adequate for derivation of an intermediate-duration oral MRL. No dose-response data are available for humans. Gavage studies of rats and mice treated for 90 days (NTP 1982) were the only available intermediate-duration oral studies in which treatment-related adverse effects were observed. Although the 90-day oral studies of NTP (1982) included histopathologic examination of multiple tissues and organs, the study report presented results only for the liver. The kidney is a known target of toxicity following inhalation exposure to 1,1-dichloroethene, particularly in mice (NTP 2015a). Additional intermediate-duration oral studies that employ exposure via drinking water or food should be designed to evaluate dose-response relationships; such studies should evaluate a comprehensive set of endpoints, including the liver and kidney.

Chronic-Duration MRLs. The database was considered adequate for derivation of a chronic-duration inhalation MRL for 1,1-dichloroethene based on histopathologic nasal lesions in mice (NTP 2015a). A similarly designed study of rats employed a higher range of exposure levels (25–100 ppm) than those employed in the study of mice (6.25–25 ppm). In the rat study, nasal lesions were observed at all exposure concentrations. The potential for 1,1-dichloroethene-induced nasal lesions in rats chronically exposed to 1,1-dichloroethene vapor at exposure concentrations <25 ppm represents a data gap. Relatively few chronic-duration oral studies are available for 1,1-dichloroethene. Most chronic-duration oral studies employed relatively low doses; for many evaluated endpoints, the highest dose level represented a NOAEL. Additional chronic-duration oral studies could be performed at higher dose levels to ensure that maximum tolerated dose levels are achieved. However, the database was considered sufficient to derive a chronic-duration oral MRL for 1,1-dichloroethene.

Health Effects.

Immunological. 1,1-Dichloroethene-induced effects on the immune system have not been studied in humans; limited animal data are available. Investigations including measures of immunocompetence and histopathological observations of animal organs and tissues involved in immunological response would provide valuable information. Additional dermal sensitization studies in animals might provide information on whether 1,1-dichloroethene is likely to cause an allergic response.

Genotoxic. No studies were identified that evaluated genotoxic effects of 1,1-dichloroethene in humans following any route of exposure. Several *in vitro* studies suggest that 1,1-dichloroethene, only in the presence of activating systems, is mutagenic in both prokaryotic and eukaryotic organisms. These results are consistent with the idea that a reactive metabolic intermediate(s), and not the parent compound, is (are) responsible for the genotoxic properties of 1,1-dichloroethene. Results from *in vivo* rodent assays that employed inhalation or oral exposure to 1,1-dichloroethene found no evidence for 1,1-dichloroethene-related effects on micronuclei in mouse peripheral blood erythrocytes (NTP 2015a), micronuclei in mouse bone marrow or fetal liver or blood (Sawada et al. 1987), chromosomal aberrations in rat bone marrow (Rampy et al. 1977), or dominant lethality in rats (Short et al. 1977c) or mice (Andersen et al. 1977). A weakly positive response was obtained for DNA damage in mouse kidney cells (Reitz et al. 1980). The genotoxic potential of 1,1-dichloroethene has been adequately assessed.

Epidemiological and Human Dosimetry Studies. Most of the available information on the adverse effects of 1,1-dichloroethene in humans comes from cases of acute poisoning occurring primarily in the workplace. Limitations inherent in these studies typically include unquantified exposure levels and durations, as well as concomitant exposure to other toxic substances. The few available industrial surveys and epidemiological studies are limited in their usefulness because of small sample size, short follow-up periods, and/or brief exposure periods. Despite their inadequacies, studies in humans indicate that 1,1-dichloroethene can cause central nervous system effects and irritation of the mucous membranes (EPA 1979; Quast et al. 1986). Well-controlled epidemiological studies of people living near areas where 1,1-dichloroethene has been detected in surface water and groundwater, near industries releasing 1,1-dichloroethene, and near hazardous waste sites, as well as occupationally-exposed people could add to and clarify the existing limited database on 1,1-dichloroethene-induced human health effects.

Biomarkers of Exposure and Effect.

Exposure. Information regarding populations exposed specifically to 1,1-dichloroethene is not available; therefore, no known biomarker of exposure to 1,1-dichloroethene has been identified in humans. However, if 1,1-dichloroethene is metabolically disposed of by humans in a way similar to that observed in animals, 1,1-dichloroethene in expired air could be a biomarker of recent exposure to relatively high concentrations of 1,1-dichloroethene. Similarly, urinary excretion of metabolites such as thioglycolic acid could also be considered a biomarker of recent exposure. Such urinary metabolites would not be specific biomarkers for 1,1-dichloroethene exposure because other chemicals produce similar urinary

metabolites. Hence, the development of methods to detect alternative biomarkers specific to 1,1-dichloroethene exposure would be useful.

Effect. Information regarding populations exposed specifically to 1,1-dichloroethene is not available. Research leading to the identification of specific DNA adducts formed after 1,1-dichloroethene exposure would be valuable. This would facilitate medical surveillance leading to early detection of potentially adverse health effects and possible treatment.

Absorption, Distribution, Metabolism, and Excretion. There are no quantitative data regarding the toxicokinetics of 1,1-dichloroethene in humans by inhalation, oral, or dermal routes. The animal data indicate that 1,1-dichloroethene is efficiently absorbed by the inhalation (Dallas et al. 1983; McKenna et al. 1978a) and oral routes (Jones and Hathway 1978a; McKenna et al. 1978b; Putcha et al. 1986). These studies have been conducted mostly in rats and mice. Dermal absorption data are lacking, but limited absorption by this route should be anticipated based on the physical and chemical properties of 1,1-dichloroethene and the fact that 1,1-dichloroethene was positive for initiation of papillomas in an initiation/promotion study of dermally-treated mice (Van Duuren et al. 1979). Furthermore, human and rodent studies of other halocarbons such as trichloroethylene have demonstrated that percutaneous absorption occurs (McDougal et al. 1990).

Animal data regarding inhalation exposure (Jaeger et al. 1977) and oral exposure (Jones and Hathway 1978c) to 1,1-dichloroethene demonstrate the distribution of 1,1-dichloroethene and/or its metabolites to the liver, kidney, and lung. Additional data on the distribution of 1,1-dichloroethene and its metabolites would be useful. Studies regarding distribution through the placenta were not available. However, another halocarbon, trichloroethylene, has been demonstrated to readily cross the placenta (Fisher et al. 1989).

The metabolism of 1,1-dichloroethene has been extensively studied in rats and mice following inhalation and oral exposure (Jones and Hathway 1978a, 1978c; McKenna et al. 1977, 1978b; Reichert et al. 1979). Experimental evidence indicates that the metabolism of 1,1-dichloroethene is a saturable process. Although information regarding metabolism following dermal exposure is lacking, there is no reason to believe that other pathways would operate following dermal exposure. Human toxicokinetic data are needed to evaluate the metabolic fate of 1,1-dichloroethene. The use of human cell systems and tissues in culture could serve as an alternative to studying the metabolic fate of 1,1-dichloroethene in humans.

Comparative Toxicokinetics. Limited *in vitro* data suggest that 1,1-dichloroethene toxicokinetic properties in humans may be similar to those observed in animals. Toxicokinetic studies in rats and mice suggest that no qualitative differences exist between these two species, although metabolism of 1,1-dichloroethene to toxic kidney metabolites are more prominent in mice than rats (Jones and Hathway 1978a, 1978c; McKenna et al. 1977, 1978b; Reichert et al. 1979). Experiments in animals (mostly rats and mice) indicate that the liver, kidney, and lungs are common target organs across species. Additional quantitative data on metabolic activation and inactivation of 1,1-dichloroethene in human liver, kidney, and lung could be used to evaluate the human relevance of mouse and rat cytotoxicity and carcinogenicity findings. The human data could be used to develop and validate a human PBPK/PD model for 1,1-dichloroethene.

Children's Susceptibility. No data were located to suggest significant age-related differences in susceptibility to 1,1-dichloroethene toxicity.

Physical and Chemical Properties. The physical and chemical properties of 1,1-dichloroethene have been adequately characterized (see Table 4-2). No data needs are identified.

Production, Import/Export, Use, Release, and Disposal. 1,1-Dichloroethene is produced commercially. Information on production, uses, and releases of this chemical is available and have been discussed in Chapter 5. Additional information on the current criteria for land treatment or burial and on the amounts of 1,1-dichloroethene disposed of by incineration versus landfilling would be insightful.

Environmental Fate. Sufficient data exist to show that hydrolysis is not significant in determining the half-life in aqueous media. The available data suggest that 1,1-dichloroethene can undergo transformation by reaction with radical species in the atmosphere and biodegradation under certain conditions in water and soil/sediments as discussed in Section 5.4.2. The atmospheric half-life of 1,1-dichloroethene in air following hydroxyl radical reaction is estimated to be 4–20 hours, and the products of this reaction are highly toxic phosgene, formaldehyde, and chloroacetyl chloride (Tuazon et al. 1988). The estimated half-life for hydrolysis of 1,1-dichloroethene at 25°C under neutral conditions is $1.2x10^8$ years (Jeffers et al. 1989). 1,1-Dichloroethene is reduced to vinyl chloride under various conditions in groundwater and sediment. In a methane-utilizing culture from lake sediment, 1,1-dichloroethene was degraded under aerobic conditions within 2 days; the end products, although unspecified, did not include vinyl chloride. Additional studies are needed to characterize aerobic and

anaerobic transformation processes in soils and water and to quantify degradation rates relevant to environmental conditions in these media.

Bioavailability from Environmental Media. The monitoring data available indicate that 1,1-dichloroethene is present in some samples of air, water, soil, and foodstuffs. Animal studies indicate that 1,1-dichloroethene is well absorbed following inhalation and oral exposure. 1,1-Dichloroethene and its metabolites can be measured in the breath, blood, urine, and adipose tissue of humans. While EPA's STORET database contains considerable water monitoring data, there are problems with the database that limit its usefulness. The detection limit is often recorded when no chemical is detected, with and without indication, so it is difficult to gain meaningful figures for surface water and groundwater concentrations representative of positive determinations to evaluate potential exposure scenarios. It would be helpful, when quantitative data cannot be obtained, if these monitoring data would indicate whether or not this chemical was qualitatively detected in the samples.

Food Chain Bioaccumulation. No information was found regarding the bioconcentration of 1,1-dichloroethene in plants, aquatic organisms, or animals. On the basis of the log octanol/water partition coefficient value of 2.13 (EPA 1982), bioconcentration of the compound to significant levels by terrestrial or aquatic organisms is not expected. No data were located regarding the biomagnification of 1,1-dichloroethene in terrestrial or aquatic food chains. Given the expected limited bioconcentration (CITI 1992) of the compound, the potential for biomagnification in terrestrial and aquatic food chains is very low. Additional experimental data to confirm this predicted limited food chain bioaccumulation of 1,1-dichloroethene would be helpful in evaluating the relative significance of this source of exposure.

Exposure Levels in Environmental Media. Data on the concentrations of 1,1-dichloroethene in surface water, soil, and food are limited. Continued monitoring would be beneficial in assessing the potential risk of environmental exposure. Reliable monitoring data for the levels of 1,1-dichloroethene in contaminated media at hazardous waste sites are needed so that the information obtained on levels of 1,1-dichloroethene in the environment can be used in combination with the known body burden of 1,1-dichloroethene to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. 1,1-Dichloroethene was included in NHANES for study years 2003–2004 and 2005–2006, where it was not found above the limit of detection. As a chemical used in the production of materials intended for food applications, continued biological monitoring of populations

would lend insight in assessing potential risk of deleterious effects from exposures. Additional information on potential exposures resulting from residence in the vicinity of hazardous waste sites would provide a more accurate characterization of human exposure in the United States.

Exposures of Children. Children may be exposed to 1,1-dichloroethene through the same routes as adults. Occupationally exposed workers are at greater risk of exposure to higher levels of this chemical than the general U.S. population.

6.3 ONGOING STUDIES

No ongoing studies were identified by the National Institutes of Health (NIH) (RePORTER 2020).

CHAPTER 7. REGULATIONS AND GUIDELINES

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

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

Agency	Description	Information	Reference
	Air		
EPA	RfC	$2x10^{-1}$ mg/m^3 (0.05 ppm)	IRIS 2005
WHO	Air quality guidelines	Not listed	WHO 2010
	Water & Food		
EPA	Drinking water standards and health advisories		EPA 2018a
	1-Day health advisory (10-kg child)	2 mg/L	
	10-Day health advisory (10-kg child)	1 mg/L	
	DWEL	2 mg/L	
	Lifetime health advisory	0.4 mg/L	
	10^{-4} Cancer risk	0.006 mg/L	
	National primary drinking water regulations		EPA 2009b
	MCL and public health goal	0.007 mg/L	
	RfD	$5x10^{-2}$ mg/kg/day	IRIS 2005
WHO	Drinking water quality guidelines	Not established	WHO 2017
FDA	Substances Added to Food	Not listed[a]	FDA 2020c
	List of Indirect Additives Used in Food Contact Substances	Approved under indirect additives regulations	FDA 2019
	Allowable level in bottled water	0.007 mg/L	FDA 2017
	Cancer		
HHS	Carcinogenicity classification	No data	NTP 2016
EPA	Carcinogenicity classification	Group C[b,c]	IRIS 2005
IARC	Carcinogenicity classification	Group 2B[d]	IARC 2019
	Occupational		
ACGIH	TLV (TWA)—air	5 ppm (20 mg/m^3)	ACGIH 2001
OSHA	PEL (8-hour TWA) for general industry, shipyards, and construction—air	No data	OSHA 2019a, 2019b, 2019c

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

Agency	Description	Information	Reference
NIOSH	REL (up to 10-hour TWA)	Ca[e]	NIOSH 2019
	IDLH	Ca[e]	
	Emergency Criteria		
EPA	AEGLs-air	Not listed	EPA 2018b
DOE	PACs-air		DOE 2018a
	PAC-1[f]	45 ppm	
	PAC-2[f]	500 ppm	
	PAC-3[f]	1,000 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 in food, delisted color additives, and some substances "no longer FEMA GRAS".
[b]Group C: possible human carcinogen.
[c]Suggestive evidence of carcinogenicity via the inhalation route, but not sufficient evidence to assess human carcinogenic potential following inhalation exposure. Data are inadequate for an assessment of human carcinogenic potential via the oral route.
[d]Group 2B: possibly carcinogenic to humans.
[e]Potential occupational carcinogen.
[f]Definitions of PAC terminology are available from U.S. Department of Energy (DOE 2018b).

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; DOE = Department of Energy; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; 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 concentration; 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; TLV = threshold limit values; TWA = time-weighted average; WHO = World Health Organization

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APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

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

MRLs are derived for hazardous substances using the NOAEL/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (≥365 days) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. 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 S102-1, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,1-Dichloroethene
CAS Numbers: 75-35-4
Date: April 2022
Profile Status: Final
Route: Inhalation
Duration: Acute

MRL Summary: Available data were not considered adequate for derivation of an acute-duration inhalation MRL for 1,1-dichloroethene.

Rationale for Not Deriving an MRL: No exposure-response human data are available. The lowest LOAEL for acute-duration inhalation exposure of laboratory animals is a serious LOAEL of 15 ppm for a study in which death and maternal body weight loss occurred in rats exposed to 1,1-dichloroethene vapor for 22–23 hours/day during GDs 6–16 (EPA 1977a).

Agency Contacts (Chemical Managers): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,1-Dichloroethene
CAS Numbers: 75-35-4
Date: March 2022
Profile Status: Final
Route: Inhalation
Duration: Intermediate
MRL 0.001 ppm (1 ppb)
Critical Effect: Necrosis in nasal olfactory epithelium
Reference: NTP 2015a
Point of Departure: $BMCL_{10}$ of 1.59 ppm ($BMCL_{HEC}$ of 0.036 ppm)
Uncertainty Factor: 30
LSE Graph Key: 40
Species: Rat

MRL Summary: An intermediate-duration inhalation MRL of 0.001 ppm (1 ppb) has been derived for 1,1-dichloroethene based on increased incidences of necrosis in nasal olfactory epithelium of male F344/N rats exposed to 1,1-dichloroethene vapor for 6 hours/day, 5 days/week for 14 weeks (NTP 2015a). The MRL is based on a $BMCL_{10}$ of 1.59 ppm, which was adjusted to continuous duration exposure and converted to a human equivalent concentration ($BMCL_{HEC}$) of 0.036 ppm and divided by a total uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability).

Selection of the Critical Effect: No exposure-response human data are available. Table A-1 summarizes candidate critical effects from intermediate-duration inhalation studies in laboratory animals. The lowest LOAEL is 6.25 ppm for nasal lesions in male and female rats, depressed body weight gain in female mice, and increased relative kidney weight in female mice exposed to 1,1-dichloroethene vapor for 6 hours/day, 5 days/week for 14 weeks (NTP 2015a). The kidney weight increase at 6.25 ppm in female mice is of questionable toxicological significance because it occurred in the absence of exposure-related increases in histopathologic kidney lesions. Seriously depressed body weight gain was reported at all exposure levels (6.25–100 ppm) among the female mice (27–41% less than that of controls) and at exposure concentrations ≥12.5 ppm among the male mice (24–38% less than that of controls). Mean final body weights of the 6.25, 12.5, 25, 50, and 100 ppm groups of female mice were 12, 9, 12, 18, and 15%, respectively, less than that of controls. Mean final body weights of the 12.5, 25, and 50 ppm groups of male mice were 10, 15, and 16%, respectively, less than that of controls. However, in a similarly designed 105-week study, there were no effects on body weight in the male or female mice during the first 13 weeks of exposures at 6.25, 12.5, or 25 ppm (NTP 2015a). Body weight effects in the female mice of the 14-week study were not considered as a critical effect for MRL derivation because the female mouse body weight data from the 2-year study (for weeks 1–13, 14–52, and 53–103) did not corroborate the result from the 14-week study.

The nasal lesions in the male and female rats were selected to represent the critical effects of intermediate-duration inhalation exposure to 1,1-dichloroethene because they represent the lowest reliable LOAEL (6.25 ppm).

Table A-1. Summary of Candidate Critical Effects for Deriving an Intermediate-Duration Inhalation MRL for 1,1-Dichloroethene

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Body weight effects					
B6C3F1/N mouse	14 weeks (5 days/week 6 hours/day)	ND F	6.25 F	Depressed body weight gain	NTP 2015a
Respiratory effects					
F344/N rat	14 weeks (5 days/week 6 hours/day)	ND	6.25	Lesions in olfactory epithelium	NTP 2015a
B6C3F1/N mouse	14 weeks (5 days/week 6 hours/day)	6.25	12.5	Increased lung weight	NTP 2015a
Hepatic effects					
F344/N rat	14 weeks (5 days/week 6 hours/day)	6.25 M	12.5 M	Hepatic centrilobular cytoplasmic alterations	NTP 2015a
Renal effects					
B6C3F1/N mouse	14 weeks (5 days/week 6 hours/day)	6.25 M ND F	12.5 M 6.25 F	M: nephropathy F: increased kidney weight	NTP 2015a

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

Selection of the Principal Study: The 14-week inhalation study in rats (NTP 2015a) identified the lowest less serious LOAEL (6.25 ppm) for 1,1-dichloroethene exposure-related effects considered to be toxicologically significant. Therefore, the 14-week inhalation study of rats (NTP 2015a) was selected as the principal study for deriving an intermediate-duration inhalation MRL.

Summary of the Principal Study:

NTP. 2015a. NTP technical report on the toxicology and carcinogenesis studies of vinylidene chloride (CAS No. 75-35-4) in F344/N rats and B6C3F1/N mice (inhalation studies). NTP TR 582. National Toxicology Program. Research Triangle Park, NC: U.S. Department of Health and Human Services.

Groups of F344/N rats (10/sex/group; 5–7 weeks of age) were exposed (whole body) to 1,1-dichloroethene vapor for 6 hours/day (+10 minutes), 5 days/week for 14 weeks at 0, 6.25, 12.5, 25, 50, or 100 ppm. Evaluations included survival, clinical signs, body weight, hematology, clinical chemistry, selected organ weights, and gross and histopathology. The following targets of toxicity were identified:

- ***Respiratory:*** There were no exposure-related effects on lung weight. Significantly increased incidences of selected nasal lesions were observed in both males and females. Incidence data are presented in Table A-2. Olfactory epithelium atrophy, mineralization, and necrosis occurred in males and females at all exposure levels; none of these lesions occurred in control males or females.

- ***Hepatic:*** Hepatic centrilobular cytoplasmic alterations were observed in males at 12.5 ppm (6/10 rats) and all males at higher exposure levels. Exposure-related liver lesions in female rats were limited to hepatocellular cytoplasmic vacuolization in all females exposed at 50 and 100 ppm.

- ***Renal:*** Slightly increased relative kidney weights were noted in males at 6.25, 12.5, and 100 ppm (3–7% greater than controls), but not at 25 or 50 ppm. Females exhibited exposure concentration-related significantly increased relative kidney weights at exposure levels ≥12.5-ppm (6–16% greater than controls). There was no evidence of exposure-related increased incidences of renal lesions in males or females (NOAEL of 100 ppm).

- ***Reproductive:*** At the highest exposure level (100 ppm), males exhibited 5% decreased sperm motility and 15–16% decreased spermatid count.

Table A-2. Selected Nasal Lesion Incidences in Male and Female F344/N Rats Exposed to 1,1-Dichloroethene for 6 Hours/Day, 5 Days/Week for 14 Weeks

	1,1-Dichloroethene exposure level (ppm)					
Lesion type	0	6.25	12.5	25	50	100
Males						
Olfactory epithelium						
Atrophy	0/10[a]	4/10[b] (1.0)	10/10[c] (1.0)	10/10[c] (1.7)	10/10[c] (2.2)	10/10[c] (2.7)
Mineralization[d]	0/10	10/10[c] (1.3)	10/10[c] (2.0)	10/10[c] (2.9)	10/10[c] (3.0)	10/10[c] (2.6)
Necrosis	0/10	2/10 (1.0)	6/10[c] (1.0)	9/10[c] (1.0)	7/10[c] (1.7)	10/10[c] (1.6)
Turbinate						
Atrophy	0/10	0/10	10/10[c] (1.0)	10/10[c] (2.0)	10/10[c] (2.3)	10/10[c] (3.0)
Females						
Olfactory epithelium						
Atrophy	0/10	2/10 (1.0)	10/10[c] (1.0)	10/10[c] (1.3)	10/10[c] (1.7)	10/10[c] (2.4)
Mineralization[d]	0/10	5/10[b] (1.0)	9/10[c] (1.3)	10/10[c] (1.9)	10/10[c] (2.1)	10/10[c] (2.3)
Necrosis	0/10	1/10 (1.0)	3/10 (1.3)	6/10[c] (1.5)	10/10[c] (2.2)	10/10[c] (3.0)
Turbinate						
Atrophy	0/10	0/10	10/10[c] (1.0)	10/10[c] (2.0)	10/10[c] (2.2)	10/10[c] (3.0)
Males and females (combined incidences)						
Olfactory epithelium						
Atrophy	0/20	6/20[e]	20/20[f]	20/20[f]	20/20[f]	20/20[f]
Mineralization[d]	0/20	15/20[f]	19/20[f]	20/20[f]	20/20[f]	20/20[f]
Necrosis	0/20	3/20	9/20[f]	15/20[f]	17/20[f]	20/20[f]
Turbinate						
Atrophy	0/20	0/20	20/20[f]	20/20[f]	20/20[f]	20/20[f]

[a]Incidence (severity;1 = minimal, 2 = mild, 3 = moderate, 4 = marked).
[b]Significantly different from chamber control incidence by the Poly-3 test ($p<0.05$).
[c]Significantly different from chamber control incidence by the Poly-3 test ($p<0.01$).
[d]Mineralization was described as "deposits of greyish-blue material in the basement membrane, often underlying an atrophic epithelium or disrupting the epithelium, and most often affecting the lateral walls and turbinates." The deposits were not actually within the olfactory epithelium and of unknown toxicological significance.
[e]Significantly different from chamber control incidence by Fisher's exact test ($p<0.05$) performed by SRC, Inc.
[f]Significantly different from chamber control incidence by Fisher's exact test ($p<0.01$) performed by SRC, Inc.

Source: NTP 2015a

Selection of the Point of Departure for the MRL: A $BMCL_{10}$ of 1.59 ppm for olfactory epithelium necrosis in male rats estimated from the frequentist-restricted 3-degree Multistage model was selected as the point of departure (POD) for the intermediate-duration inhalation MRL for 1,1-dichloroethene.

The lowest LOAEL identified in the NTP (2015a) 14-week rat study was 6.25 ppm for increased incidence of nasal lesions in males and females. Within olfactory epithelium, atrophy and necrosis were observed at the lowest exposure level tested (6.25 ppm). Deposits of greyish-blue material in the basement membrane, often underlying an atrophic epithelium or disrupting the epithelium, and most often affecting the lateral walls and turbinates, were reported as mineralization in olfactory epithelium. Although these deposits occurred at 100% incidence in all groups of 1,1-dichloroethene-exposed male rats and at 50% in the 6.25 ppm females and 100% in all other exposed groups of females, their occurrence within the region of the basement membrane (rather than the olfactory epithelium) is of questionable toxicological significance. Therefore, mineralization was not considered as a candidate critical effect for deriving an intermediate-duration inhalation MRL for 1,1-dichloroethene. However, atrophy and necrosis are considered reliable exposure-related adverse effects and were considered candidate critical effects. Atrophy in the turbinates was not considered as a candidate critical effect because this lesion was not observed at the lowest exposure level (6.25 ppm).

The incidence data for atrophy and for necrosis in the olfactory epithelium of the male and the female rats were fit to all standard dichotomous models in the EPA Benchmark Dose Software (BMDS, version 3.1.2) using a benchmark response (BMR) of 10% change in incidence from controls. Based on relatively similar male and female exposure concentration-response data for atrophy and for necrosis in olfactory epithelium, incidence data for both sexes were also combined to increase the statistical power of the benchmark result. Analysis of the data for necrosis in males and females using EPA's Categorical Regression Analysis (Cater 3.1) software confirmed the acceptability of combining male and female incidence data. Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), scaled residuals (within ±2 units) at the data points (except the control) closest to the predefined BMR, BMCL values that are not 10 times lower than the lowest non-zero dose, and visual inspection of the proximity of the predicted dose-response curve to the observed data points closest to the BMR. For each dataset, among all models providing adequate fit to the data, the lowest BMCL was selected as the POD when the difference between the BMCLs estimated from these models was >3-fold; otherwise, the BMCL from the model with the lowest Akaike Information Criterion (AIC) was chosen.

Model predictions for nasal olfactory epithelium atrophy in the male rats are presented in Table A-3. Most models provided adequate fit to the data; the multistage 1-degree and Weibull models did not provide adequate fit because the BMDL was 10 times lower than the lowest non-zero concentration and because the lower limited includes zero, respectively. The $BMCL_{10}$ values varied by >3-fold; therefore, the lowest $BMCL_{10}$ (0.73 ppm) considered as a potential POD.

Table A-3. Model Predictions for Incidence of Nasal Olfactory Epithelium Atrophy in Male F344/N Rats Exposed to 1,1-Dichloroethene 6 Hours/Day, 5 Days/Week for 14 Weeks (NTP 2015a)

Model	BMC_{10}[a] (ppm)	$BMCL_{10}$[a] (ppm)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose near BMC	Control group
Dichotomous Hill	4.74	2.85	0.997	17.76	-6.96×10^{-2}	-3.90×10^{-4}
Gamma[d]	3.85	1.69	0.981	18.21	-2.69×10^{-1}	-3.90×10^{-4}
Log-Logistic[e]	4.74	2.85	1.000	15.76	-6.96×10^{-2}	-3.90×10^{-4}
Multistage Degree 5[f,g]	**3.81**	**0.73**	**1.000**	**15.53**	$\mathbf{-7.19 \times 10^{-2}}$	$\mathbf{-3.90 \times 10^{-4}}$
Multistage Degree 4[f]	3.79	0.74	1.000	15.55	-8.79×10^{-2}	-3.90×10^{-4}
Multistage Degree 3[f]	3.55	0.83	1.000	15.72	-2.30×10^{-1}	-3.90×10^{-4}
Multistage Degree 2[f]	2.37	0.74	0.952	17.13	-3.90×10^{-4}	-3.90×10^{-4}
Multistage Degree 1[f]			0.529	20.95	-3.90×10^{-4}	-3.90×10^{-4}
Weibull[c]			0.833	19.74	-4.16×10^{-4}	-4.16×10^{-4}
Logistic	4.46	2.26	1.000	15.54	-1.02×10^{-2}	-1.14×10^{-1}
Log-Probit	5.35	2.85	1.000	15.46	-1.13×10^{-4}	-3.90×10^{-4}
Probit	2.16	1.37	0.673	21.26	-1.09	-1.09

[a]BMC and BMCL 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 for dose group near the BMC and for the control dose group.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]Recommended model. Most models provided adequate fit to the data. BMCLs for models providing adequate fit were not sufficiently close (differed by >3-fold). Therefore, the model with lowest BMCL was selected (Multistage 5 degree model).

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

Model predictions for nasal olfactory epithelium atrophy in the female rats are presented in Table A-4. The 1-degree Multistage model (the BMCL is 10 times lower than the lowest non-zero dose) and the Weibull model (lower limit includes zero) provided inadequate fit to the data. Visual inspection of the 2-degree Multistage model revealed relatively poor correlation between predicted incidence and observed incidence in the region corresponding to the two experimental data points closest to the control value; therefore, the model fit was considered inadequate. All other models provided adequate fit to the data as judged by goodness-of-fit p-value and scaled residual criteria. The $BMCL_{10}$ of 3.48 ppm from the model with the lowest AIC (Logistic model) was selected as a potential POD based on nasal olfactory epithelium atrophy in the female rats because the $BMCL_{10}$ values estimated from models with adequate varied by <3-fold.

Table A-4. Model Predictions for Incidence of Nasal Olfactory Epithelium Atrophy in Female F344/N Rats Exposed to 1,1-Dichloroethene 6 Hours/Day, 5 Days/Week for 14 Weeks (NTP 2015a)

Model	BMC_{10}[a] (ppm)	$BMCL_{10}$[a] (ppm)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose near BMC	Control group
Dichotomous Hill	5.46	4.15	0.997	12.60	-1.60×10^{-1}	-3.90×10^{-4}
Gamma[d]	4.72	3.19	0.892	15.88	-5.66×10^{-1}	-3.92×10^{-4}
Log-Logistic[e]	5.46	4.15	0.989	14.60	-1.60×10^{-1}	-3.90×10^{-4}
Multistage Degree 5[f]	4.72	1.49	0.996	12.62	-3.56×10^{-1}	-3.90×10^{-4}
Multistage Degree 4[f]	4.63	1.49	0.994	12.74	-4.17×10^{-1}	-3.90×10^{-4}
Multistage Degree 3[f]	4.05	1.68	0.950	13.66	-8.21×10^{-1}	-3.90×10^{-4}
Multistage Degree 2[f,g]	2.76	1.26	0.661	16.59	-3.90×10^{-4}	-3.90×10^{-4}
Multistage Degree 1[f]			0.152	22.55	-3.90×10^{-4}	-3.90×10^{-4}
Weibull[c]			0.493	19.06	-4.96×10^{-4}	-4.96×10^{-4}
Logistic[h]	**5.40**	**3.48**	**1.000**	**12.17**	$\mathbf{-5.34 \times 10^{-2}}$	$\mathbf{-7.10 \times 10^{-2}}$
Log-Probit	5.86	4.35	1.000	14.01	-7.59×10^{-4}	-3.90×10^{-4}
Probit	2.80	1.74	0.454	19.69	-8.49×10^{-1}	-8.49×10^{-1}

[a]BMC and BMCL 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 for dose group near the BMC and for the control dose group.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]Visual inspection of the 2-degree Multistage model fit revealed relatively poor correlation between predicted incidence and observed incidence in the region corresponding to the two experimental data points close to the control value and the model fit was considered inadequate.
[h]Recommended model. Most models provided adequate fit to the data. BMCLs for models providing adequate fit were not sufficiently close (differed by >3-fold). Among the models providing adequate fit, the model with the lowest AIC was selected (Logistic).

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

Model predictions for combined incidences of nasal olfactory epithelium atrophy in the male and female rats are presented in Table A-5. The 1-degree Multistage model provided inadequate fit to the dataset (goodness-of-fit p-value <0.1). All other models provided adequate fit to the data. The Log-Probit model $BMCL_{10}$ of 4.29 ppm (model with the lowest AIC) was selected as a potential POD based on combined incidences of nasal olfactory epithelium atrophy in the male and female rats.

Table A-5. Model Predictions for Incidence of Nasal Olfactory Epithelium Atrophy in Male and Female F344/N Rats Exposed to 1,1-Dichloroethene 6 Hours/Day, 5 Days/Week for 14 Weeks (NTP 2015a)

Model	BMC_{10}[a] (ppm)	$BMCL_{10}$[a] (ppm)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose near BMC	Control group
Dichotomous Hill	5.07	4.15	0.981	29.25	-1.42×10^{-1}	-5.52×10^{-4}
Gamma[d]	4.27	3.24	0.852	30.80	-5.53×10^{-1}	-5.54×10^{-4}
Log-Logistic[e]	5.07	4.15	0.981	29.25	-1.42×10^{-1}	-5.52×10^{-4}
Multistage Degree 5[f]	4.23	1.45	0.998	26.90	-2.51×10^{-1}	-5.52×10^{-4}
Multistage Degree 4[f]	4.18	1.50	0.997	27.00	-3.00×10^{-1}	-5.52×10^{-4}
Multistage Degree 3[f]	3.81	1.89	0.967	27.87	-6.75×10^{-1}	-5.52×10^{-4}
Multistage Degree 2	2.56	1.49	0.408	34.12	-5.52×10^{-4}	-5.52×10^{-4}
Multistage Degree 1[f]			0.019	43.82	-5.71×10^{-4}	-5.71×10^{-4}
Weibull[c]	2.40	2.40	0.339	35.29	-5.53×10^{-4}	-5.53×10^{-4}
Logistic	4.89	3.46	1.000	26.65	-3.47×10^{-2}	-1.30×10^{-1}
Log-Probit[g]	**5.58**	**4.29**	**1.000**	**26.44**	$\mathbf{-3.03 \times 10^{-4}}$	$\mathbf{-5.52 \times 10^{-4}}$
Probit	2.46	1.76	0.190	39.36	-1.37	-1.37

[a]BMC and BMCL 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 for dose group near the BMC and for the control dose group.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]Recommended model. Most models provided adequate fit to the data. BMCLs for models providing adequate fit were sufficiently close (differed by <3-fold) and the model with the lowest AIC was selected. Therefore, the Log-Probit is the recommended model.

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

Model predictions for nasal olfactory epithelium necrosis in the male rats are presented in Table A-6. The Gamma, 5-degree Multistage, 1-degree Multistage, Weibull, Logistic, and Probit models provided inadequate fit to the dataset (goodness-of-fit p-value <0.1); the Log-Probit model also did not provide adequate fit (BMCL was 10 times lower than the lowest non-zero dose). Among the models providing adequate fit to the data, the $BMCL_{10}$ of 1.59 ppm from the model with the lowest AIC (2-degree Multistage) was selected as a potential POD because the $BMCL_{10}$ values varied by <3-fold.

Table A-6. Model Predictions for Incidence of Nasal Olfactory Epithelium Necrosis in Male F344/N Rats Exposed to 1,1-Dichloroethene 6 Hours/Day, 5 Days/Week for 14 Weeks (NTP 2015a)

Model	BMC_{10}[a] (ppm)	$BMCL_{10}$[a] (ppm)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose near BMC	Control group
Dichotomous Hill	4.82	0.79	0.112	55.22	$3.96x10^{-2}$	$-3.92x10^{-4}$
Gamma[d]			0.085	53.29	$-3.98x10^{-4}$	$-3.98x10^{-4}$
Log-Logistic[e]	2.53	0.72	0.207	51.85	$-3.90x10^{-4}$	$-3.90x10^{-4}$
Multistage Degree 5[f]			0.086	53.29	$-3.90x10^{-4}$	$-3.90x10^{-4}$
Multistage Degree 4[f]	2.23	1.59	0.147	51.29	$-3.90x10^{-4}$	$-3.90x10^{-4}$
Multistage Degree 3[f]	**2.23**	**1.59**	**0.147**	**51.29**	**$-3.90x10^{-4}$**	**$-3.90x10^{-4}$**
Multistage Degree 2[f,g]	**2.23**	**1.59**	**0.147**	**51.29**	**$-3.90x10^{-4}$**	**$-3.90x10^{-4}$**
Multistage Degree 1[f]			0.085	53.29	$-3.91x10^{-4}$	$-3.91x10^{-4}$
Weibull[c]			0.085	53.29	$-4.24x10^{-3}$	$-4.24x10^{-3}$
Logistic			0.013	60.60	$-6.67x10^{-1}$	-1.66
Log-Probit			0.119	53.91	$-3.90x10^{-4}$	$-3.90x10^{-4}$
Probit			0.015	60.84	$-6.67x10^{-1}$	-1.67

[a]BMC and BMCL 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 for dose group near the BMC and for the control dose group.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]Recommended model. Five models provided adequate fit to the data. BMCLs for models providing adequate fit were sufficiently close (differed by <3-fold) and the model with the lowest AIC was selected. Therefore, the 2-degree Multistage is the recommended model.

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

Model predictions for nasal olfactory epithelium necrosis in the female rats are presented in Table A-7. All models provided adequate fit to the data as judged by goodness-of-fit p-value and scaled residual criteria. However, visual inspection of the 1-degree Multistage fit revealed relatively poor correlation between predicted incidence and observed incidence in the region corresponding to the two experimental data points closest to the control value; therefore, the model fit was considered inadequate. All other models provided adequate fit. The Probit model $BMCL_{10}$ of 5.41 ppm (corresponding to the lowest AIC among models providing adequate fit) was selected as a potential POD based on nasal olfactory epithelium necrosis in the female rats because the $BMCL_{10}$ values varied by <3-fold.

Table A-7. Model Predictions for Incidence of Nasal Olfactory Epithelium Necrosis in Female F344/N Rats Exposed to 1,1-Dichloroethene 6 Hours/Day, 5 Days/Week for 14 Weeks (NTP 2015a)

Model	BMC_{10}[a] (ppm)	$BMCL_{10}$[a] (ppm)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose near BMC	Control group
Dichotomous Hill	7.57	4.05	0.800	38.47	$4.79x10^{-1}$	$-3.90x10^{-4}$
Gamma[d]	7.03	2.97	0.852	39.29	$2.54x10^{-1}$	$-3.92x10^{-4}$
Log-Logistic[e]	7.57	4.05	0.800	38.47	$4.79x10^{-1}$	$-3.90x10^{-4}$
Multistage Degree 5[f]	5.27	2.31	0.731	42.30	$-2.01x10^{-1}$	$-1.13x10^{-3}$
Multistage Degree 4[f]	5.20	2.37	0.925	40.35	$-2.08x10^{-1}$	$-4.34x10^{-4}$
Multistage Degree 3[f]	5.44	2.49	0.974	38.45	$-1.58x10^{-1}$	$-4.08x10^{-4}$
Multistage Degree 2	6.45	2.66	0.936	38.76	$4.91x10^{-2}$	$-4.03x10^{-4}$
Multistage Degree 1[f,g] 3	2.52	1.75	0.542	40.86	$-3.91x10^{-4}$	$-3.91x10^{-4}$
Weibull[c]	6.94	3.07	0.913	38.87	$1.92x10^{-1}$	$-4.63x10^{-4}$
Logistic	8.80	5.74	0.897	37.70	$7.16x10^{-2}$	$-6.21x10^{-1}$
Log-Probit	7.40	4.16	0.831	38.16	$4.98x10^{-1}$	$-3.90x10^{-4}$
Probit[h]	8.23	5.41	0.940	37.26	$9.27x10^{-2}$	$-5.39x10^{-1}$

[a]BMC and BMCL 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 for dose group near the BMC and for the control dose group.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]The 1-degree Multistage model was judged to provide inadequate fit to the data based on visual inspection of the predicted dose-response curve.
[h]Recommended model. Among models providing adequate fit to the data, $BMCL_{10}$ values varied by <3-fold; therefore, the model with the lowest AIC was selected as the best-fitting model (Probit).

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

Model predictions for combined incidences of nasal olfactory epithelium necrosis in the male and female rats are presented in Table A-8. The Logistic and Probit models provided inadequate fit to the dataset (goodness-of-fit p-value <0.1). All other models provided adequate fit to the data. The Log-Probit model $BMCL_{10}$ of 2.57 ppm (corresponding to the lowest AIC) was selected as a potential POD based on combined incidences of nasal olfactory epithelium necrosis in the male and female rats because the $BMCL_{10}$ values varied by <3-fold.

Table A-8. Model Predictions for Incidence of Nasal Olfactory Epithelium Necrosis in Male and Female F344/N Rats Exposed to 1,1-Dichloroethene 6 Hours/Day, 5 Days/Week for 14 Weeks (NTP 2015a)

Model	BMC_{10}[a] (ppm)	$BMCL_{10}$[a] (ppm)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose near BMC	Control group
Dichotomous Hill	4.58	2.46	0.680	91.76	-1.93×10^{-1}	-5.52×10^{-4}
Gamma[d]	3.20	1.87	0.552	91.98	-6.21×10^{-1}	-7.70×10^{-3}
Log-Logistic[e]	4.58	2.46	0.680	91.76	-1.93×10^{-1}	-5.84×10^{-4}
Multistage Degree 5[f]	2.45	1.87	0.731	89.98	-5.52×10^{-4}	-5.52×10^{-4}
Multistage Degree 4[f]	2.46	1.86	0.717	90.07	-5.52×10^{-4}	-5.52×10^{-4}
Multistage Degree 3[f]	2.47	1.85	0.539	92.15	-7.06×10^{-4}	-7.06×10^{-4}
Multistage Degree 2	2.55	1.85	0.700	90.19	-5.52×10^{-4}	-5.52×10^{-4}
Multistage Degree 1[f]	2.36	1.84	0.709	90.31	-6.13×10^{-4}	-6.13×10^{-4}
Weibull[c]	2.94	1.86	0.543	92.06	-5.52×10^{-4}	-5.52×10^{-4}
Logistic			0.039	99.21	-5.87×10^{-1}	-1.67
Log-Probit[g]	**4.66**	**2.57**	**0.841**	**89.51**	$\mathbf{-2.26 \times 10^{-1}}$	$\mathbf{-5.52 \times 10^{-4}}$
Probit			0.038	99.73	-5.95×10^{-1}	-1.66

[a]BMC and BMCL 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 for dose group near the BMC and for the control dose group.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]Recommended model. Among models providing adequate fit to the data, $BMCL_{10}$ values varied by <3-fold; therefore, the model with the lowest AIC was selected as the best-fitting model (Log-Probit).

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

Best-fitting model predictions for atrophy and for necrosis in nasal olfactory epithelium of the male and female rats are presented in Table A-9. Among the best-fitting models, the lowest predicted BMC_{10} was 2.23 ppm for incidences of olfactory epithelium necrosis in the male rats estimated from the 2-degree Multistage model; the corresponding $BMCL_{10}$ of 1.59 ppm was selected as the POD. The 2-degree model is presented in Figure A-1.

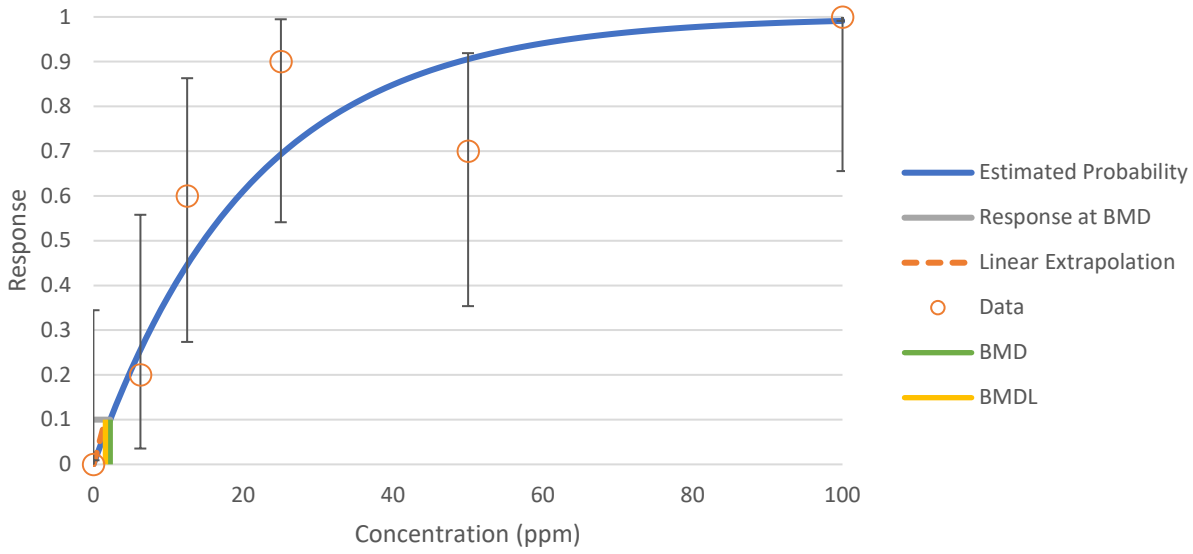
Table A-9. BMC_{10} and $BMCL_{10}$ Values from the Best-Fitting Models for Selected Nonneoplastic Lesions in Nasal Olfactory Epithelium of Male and Female F344/N Rats Exposed to 1,1-Dichloroethene 6 Hours/Day, 5 Days/Week for 14 Weeks

Lesion type	Sex	Model	BMC_{10} (ppm)	$BMCL_{10}$ (ppm)
Atrophy	Male	Multistage 5-degree	3.81	0.73
	Female	Logistic	5.40	3.48
	Combined	Log-Probit	5.58	4.29
Necrosis	**Male**	**Multistage 2-degree**	**2.23**	**1.59[a]**
	Female	Probit	8.23	5.41
	Combined	Log-Probit	4.66	2.57

[a]The $BMCL_{10}$ of 1.59 ppm for necrosis in the male rats was selected as the preferred POD for deriving an intermediate-duration inhalation MRL for 1,1-dichloroethene because it corresponds to the lowest BMC_{10} (2.23 ppm) among the group of best-fitting models for nasal olfactory epithelium lesions.

BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); POD = point of departure

Figure A-1. Fit of 2-Degree Multistage Model for Nasal Olfactory Epithelium Necrosis in Male F344/N Rats Exposed to 1,1-Dichloroethene 6 Hours/Day, 5 Days/Week for 14 Weeks



Intermittent Exposure: The $BMCL_{10}$ of 1.59 ppm was adjusted from intermittent exposure to a continuous exposure scenario according to the following equation:

$$BMCL_{ADJ} = BMCL_{10} \text{ of } 1.59 \text{ ppm} \times (6 \text{ hours}/24 \text{ hours}) \times (5 \text{ days}/7 \text{ days}) = 0.28 \text{ ppm}$$

Human Equivalent Concentration: To calculate a HEC, the $BMCL_{ADJ}$ was multiplied by the regional gas dose ratio (rat:human) for the extrathoracic region of the respiratory tract ($RGDR_{ET}$). The $RGDR_{ET}$ was calculated using the following equation:

$$RGDR_{ET} = \frac{\left(\frac{V_E}{SA_{ET}}\right)A}{\left(\frac{V_E}{SA_{ET}}\right)H}$$

where:
ET = extrathoracic region
V_E = minute volume (mL/minute)
SA = surface area (cm^2)
A = animal (rat)
H = human

EPA (1994) rat and human respiratory surface area (SA) reference values for the extrathoracic region:
Human: 200 cm^2
Rat: 15.0 cm^2

EPA (1994) reference values for minute volumes (V_e):
Human: 13.8 L/minute
Rat: 0.1319 L/minute

Therefore:

$$RGDR_{ET} = \frac{\left(\frac{V_E}{SA_{ET}}\right)A}{\left(\frac{V_E}{SA_{ET}}\right)H} = \frac{\frac{131.9\ mL/min}{15\ cm^2}}{\frac{13{,}800\ mL/min}{200\ cm^2}} = 0.13$$

$BMCL_{HEC} = BMCL_{ADJ}$ x $RGDR_{ET}$ = 0.28 ppm x 0.13 = 0.036 ppm

Uncertainty Factor: The $BMCL_{HEC}$ of 0.036 ppm was divided by a total uncertainty factor of 30:

- 3 for extrapolation from animals to humans using dosimetric adjustment
- 10 for human variability

MRL = $BMCL_{HEC}$ ÷ UFs
0.036 ppm ÷ (3 x 10) = 0.0012 ppm ≈ 0.001 ppm (1 ppb)

Other Additional Studies or Pertinent Information that Lend Support to this MRL: The nasal cavity was among the most sensitive targets of toxicity in male and female F344/N rats and B6C3F1/N mice intermittently exposed to 1,1-dichloroethene vapor for 14 or 105 weeks (NTP 2015a).

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,1-Dichloroethene
CAS Numbers: 75-35-4
Date: March 2022
Profile Status: Final
Route: Inhalation
Duration: Chronic
MRL 0.001 ppm (1 ppb)
Critical Effect: Necrosis of nasal olfactory epithelium
Reference: NTP 2015a
Point of Departure: $BMCL_{10}$ of 1.59 ppm ($BMCL_{HEC}$ of 0.036 ppm)
Uncertainty Factor: 30
LSE Graph Key: 40
Species: Rat

MRL Summary: The intermediate-duration inhalation MRL of 0.001 ppm (1 ppb) was adopted as the chronic-duration inhalation MRL for 1,1-dichloroethene. The intermediate MRL is based on a $BMCL_{10}$ of 1.59 ppm for increased necrosis of the nasal olfactory epithelium in rats exposed to 1,1-dichloroethene for 14 weeks. The $BMCL_{10}$ was adjusted to continuous duration exposure and converted to a human equivalent concentration ($BMCL_{HEC}$) of 0.036 ppm and divided by a total uncertainty factor of 30 (for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability).

Selection of the Critical Effect: No exposure-response human data are available. Table A-10 summarizes candidate critical effects from chronic-duration inhalation studies in laboratory animals. Nasal lesions (nasal turbinate atrophy, hyperostosis, metaplasia of respiratory olfactory epithelium) in mice were selected as the critical effects of chronic-duration inhalation exposure to 1,1-dichloroethene because they occurred at the lowest LOAEL (6.25 ppm).

Table A-10. Summary of Candidate Critical Effects for Deriving a Chronic-Duration Inhalation MRL for 1,1-Dichloroethene

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Body weight effects					
B6C3F1/N mouse	105 weeks (5 days/week 6 hours/day)	6.25 M 12.5 F	12.5 M 25 F	Depressed body weight	NTP 2015a
Respiratory effects					
F344/N rat	105 weeks (5 days/week 6 hours/day)	ND	25[a]	Multiple types of nasal lesions	NTP 2015a
B6C3F1/N mouse	105 weeks (5 days/week 6 hours/day)	ND	6.25	Multiple types of nasal lesions	NTP 2015a
Hepatic effects					
F344/N rat	105 weeks (5 days/week 6 hours/day)	ND	25[a]	Chronic inflammation, diffuse fatty change	NTP 2015a

Table A-10. Summary of Candidate Critical Effects for Deriving a Chronic-Duration Inhalation MRL for 1,1-Dichloroethene

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Sprague-Dawley rat	18 months (5 days/week 6 hours/day)	ND	25	Midzonal fatty change at 12 months	Quast et al. 1986
Renal effects					
B6C3F1/N mouse	105 weeks (5 days/week 6 hours/day)	ND 25 F	6.25 M	Renal tubule hyperplasia at 6.25 ppm; renal cysts at 25 ppm	NTP 2015a
Swiss mouse	52 weeks (5 days/week 4 hours/day)	ND	25	Unspecified regressive lesions	Maltoni et al. 1985
Swiss mouse	52 weeks (4–5 days/week 4 hours/day)	ND	25	Abscesses and nephritis	Maltoni et al. 1985

[a]Lowest exposure concentration tested in the rats of the NTP (2015a) 2-year study.

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

Selection of the Principal Study: The 105-week inhalation study of B6C3F1/N mice (NTP 2015a) was selected as the principal study because it identified the lowest LOAEL for 1,1-dichloroethene toxicity.

Summary of the Principal Study:

NTP. 2015a. NTP technical report on the toxicology and carcinogenesis studies of vinylidene chloride (CAS No. 75-35-4) in F344/N rats and B6C3F1/N mice (inhalation studies). NTP TR 582. National Toxicology Program. Research Triangle Park, NC: U.S. Department of Health and Human Services.

Groups of B6C3F1/N mice (50/sex/group; 5-6 weeks of age) were exposed (whole body) to 1,1-dichloroethene vapor for 6 hours/day (+10 minutes), 5 days/week for 14 weeks at 0, 6.25, 12.5, or 25-ppm. Evaluations included survival, clinical signs, body weight, and gross and histopathology. The following targets of toxicity were identified:

- ***Death:*** Survival among the 6.25 and 25 ppm males was significantly greater than that controls; survival among the 6.25 and 25 ppm females was significantly less than that of controls.

- ***Body weight:*** Mean body weights of 6.25 ppm males and females were comparable to those of respective controls. Mean body weights for 12.5 and 25 ppm males were comparable to those of controls during the first 13 weeks of exposures; thereafter, mean body weights of 12.5 and 25 ppm males averaged 10–11 and 17–19%, respectively, less than controls. Mean body weight for 12.5 ppm females was within 95% that of controls throughout the study. Mean body weight of 25 ppm females was comparable to controls during the first 13 weeks of exposures and averaged 14–20% less than controls thereafter.

- ***Respiratory:*** There were no indications of exposure-related increased incidences of nonneoplastic lesions in the lungs. Significantly increased incidences of selected nasal lesions were observed in both males and females at all exposure levels tested (6.25, 12.5, and 25 ppm). Incidence data are presented in Table A-11.

- ***Renal:*** Significantly increased incidences of renal tubule hyperplasia were observed in 6.25, 12.5, and 25 ppm groups of male mice (8/50, 22/50, and 16/50, respectively; no incidences in controls). This lesion was not considered for MRL derivation because it was considered a preneoplastic lesion. At 25 ppm, increased incidence of renal casts was observed in males.

- ***Cancer:*** At all 1,1-dichloroethene exposure levels (6.25, 12.5, and 25 ppm), male mice exhibited significantly increased incidences of renal tubule adenoma, carcinoma, and adenoma or carcinoma combined. Female mice exhibited significantly increased incidences of alveolar/bronchiolar carcinoma at 12.5 ppm (but not at 25 ppm), hepatocellular carcinoma at 25 ppm, hepatocellular adenoma or carcinoma combined at 12.5 and 25 ppm, hemangiosarcoma in the liver at 25 ppm, and hemangioma or hemangiosarcoma (combined) in all organs (combined) at 25 ppm.

Table A-11. Selected Nasal Lesion Incidences in Male and Female B6C3F1/N Mice Exposed to 1,1-Dichloroethene for 6 Hours/Day, 5 Days/Week for 105 Weeks

	1,1-Dichloroethene exposure level (ppm)			
Lesion type	0	6.25	12.5	25
Males				
Hyperostosis	1/50[a] (2.0)	27/50[b] (1.3)	45/49 (2.1)	48/49 (2.2)
Olfactory epithelium metaplasia	17/50 (1.2)	39/50[b] (1.2)	47/49[b] (1.6)	48/49[b] (1.8)
Turbinate atrophy	0/50	46/50[b] (1.1)	46/49[b] (2.1)	47/49[b] (2.8)
Females				
Hyperostosis	0/50	13/50[b] (1.2)	45/50[b] (2.0)	48/50[b] (2.2)
Olfactory epithelium metaplasia	3/50 (1.0)	29/50[b] (1.1)	49/50[b] (1.6)	50/50[b] (1.9)
Turbinate atrophy	0/50	46/50[b] (1.0)	50/50[b] (2.3)	49/50[b] (2.8)
Males and females (combined incidences)				
Hyperostosis	1/100	40/100[c]	90/99[c]	96/99[c]
Olfactory epithelium metaplasia	20/100	68/100[c]	96/99[c]	98/99[c]
Turbinate atrophy	0/100	92/100[c]	96/99[c]	96/99[c]

[a]Incidence (severity;1 = minimal, 2 = mild, 3 = moderate, 4 = marked).
[b]Significantly different from chamber control incidence by the Poly-3 test ($p<0.01$).
[c]Significantly different from chamber control incidence by Fisher's exact test ($p<0.01$) performed by SRC, Inc.

Source: NTP 2015a

Selection of the Point of Departure for the MRL: A $BMCL_{10}$ of 1.46 ppm for olfactory epithelial metaplasia in female mice estimated using the frequentist unrestricted Probit model was selected as the POD for the chronic-duration inhalation MRL for 1,1-dichloroethene.

The lowest LOAEL identified in the NTP (2015a) 105-week mouse study was 6.25 ppm for increased incidence of nasal lesions in males and females. Both male and female mice exhibited significantly increased incidence of hyperostosis, metaplasia of respiratory olfactory epithelium, and turbinate atrophy

at the lowest exposure level tested (6.25 ppm). The incidence data for nasal turbinate hyperostosis and olfactory epithelium metaplasia in the male and female mice were fit to all standard dichotomous models in EPA's BMDS (version 3.1.2) using a BMR of 10% change in incidence from controls. Based on relatively similar male and female exposure concentration-response data, incidences were combined to increase the statistical power of the benchmark result; this procedure was employed for incidences of hyperostosis as well as olfactory epithelium metaplasia. Turbinate atrophy in the male and female mice was not fit to the models because 92% incidence occurred at the lowest exposure level tested. Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), scaled residuals (within ±2 units) at the data points (except the control) closest to the predefined BMR, BMCL values that are not 10 times lower than the lowest non-zero concentration, and visual inspection of the proximity of the predicted dose-response curve to the observed data points closest to the BMR. For each dataset, among all models providing adequate fit to the data, the lowest BMCL was selected as the POD when the difference between the BMCLs estimated from these models was >3-fold; otherwise, the BMCL from the model with the lowest AIC was chosen.

Model predictions for hyperostosis in the nasal cavity of the male mice are presented in Table A-12. The 3-degree Multistage and 1-degree Multistate models provided inadequate fit to the data (goodness-of-fit p-value <0.1 and BMDL 10 times lower than the lowest non-zero dose, respectively). BMCLs for models providing adequate fit differed by <3-fold. Therefore, the lowest AIC was selected as a potential POD.

Table A-12. Model Predictions for Hyperostosis in the Nasal Cavity of Male B6C3F1/N Mice Exposed to 1,1-Dichloroethene Vapor for 6 Hours/Day, 5 Days/Week for 105 Weeks (NTP 2015a)

					Scaled residuals[c]	
Model	BMC_{10}[a] (ppm)	$BMCL_{10}$[a] (ppm)	p-Value[b]	AIC	Dose near BMC	Control group
Dichotomous Hill			NA	124.27	$9.46x10^{-7}$	$6.48x10^{-7}$
Gamma[d]			0.154	124.08	$1.31x10^{-2}$	$1.31x10^{-2}$
Log-Logistic[e,f]	**2.84**	**1.66**	**0.573**	**122.57**	**$4.63x10^{-3}$**	**$4.63x10^{-3}$**
Multistage Degree 3[g]			0.106	124.91	$3.29x10^{-2}$	$3.29x10^{-2}$
Multistage Degree 2[g]			0.106	124.91	$3.29x10^{-2}$	$3.29x10^{-2}$
Multistage Degree 1[g]			0.215	123.53	$6.77x10^{-2}$	$6.77x10^{-2}$
Weibull[d]			0.134	124.41	$2.25x10^{-2}$	$2.25x10^{-2}$
Logistic			<0.0001	128.75	-1.43	-1.43
Log-Probit	2.57	1.42	0.328	123.15	$9.15x10^{-3}$	$9.15x10^{-3}$
Probit			<0.0001	134.73	-1.75	-1.75

[a]BMC and BMCL 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 for dose group near the BMC and for the control dose group.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Recommended model. Among models providing adequate fit to the data, $BMCL_{10}$ values varied by <3-fold; therefore, the model with the lowest AIC was selected as the best-fitting model (2-degree Multistage).
[g]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); NA = not applicable

None of the models provided adequate fit to the incidence data. With the exception of the Dichotomous Hill model, the models failed to meet adequate fit (p-value for goodness of fit <0.01). For the Dichotomous Hill model, the p-value for goodness of fit was near unity (0.999), suggesting a forced fit because it hits a model boundary. Thus, the BMC and BMCL estimated from the Dichotomous Hill model was questionable for use a POD for MRL derivation.

None of the models provided adequate fit to the male and female mice combined incidence data for hyperostosis (i.e., goodness-of-fit p-values <0.1 for all models).

None of the models provided adequate fit to the olfactory epithelium metaplasia data for male mice. For the Logistic and Probit models, the goodness-of-fit p-values were <0.1; for the remaining models, the BMCL was 10 times lower than the lowest non-zero dose.

Model predictions for olfactory epithelium metaplasia in the nasal cavity of the female mice are presented in Table A-13. The 1-degree and 3-degree Multistage model provided inadequate fit to the data (goodness-of-fit p-value <0.1). BMCLs for models providing adequate fit differed by <3-fold. Therefore, the $BMCL_{10}$ of 1.46 ppm was selected as a potential POD because the Probit model provided the lowest AIC among models with adequate fit to the data.

Table A-13. Model Predictions for Olfactory Epithelium Metaplasia in Female B6C3F1/N Mice Exposed to 1,1-Dichloroethene for 6 Hours/Day, 5 Days/Week for 105 Weeks (NTP 2015a)

Model	BMC_{10}[a] (ppm)	$BMCL_{10}$[a] (ppm)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose near BMC	Control group
Dichotomous Hill	3.97	2.81	0.868	106.6	$7.42x10^{-3}$	$-6.75x10^{-4}$
Gamma[d]	3.27	1.81	0.989	106.5	$1.95x10^{-4}$	$-2.00x10^{-5}$
Log-Logistic[e]	3.96	2.81	0.869	106.6	$7.06x10^{-3}$	$-9.07x10^{-4}$
Multistage Degree 3[f]			NA	108.5	$3.72x10^{-5}$	$3.72x10^{-5}$
Multistage Degree 2[f]	2.18	0.94	0.870	104.8	$5.18x10^{-2}$	$5.18x10^{-2}$
Multistage Degree 1[f]			0.023	113.4	$1.70x10^{-1}$	$1.70x10^{-1}$
Weibull[d]	2.53	1.39	0.996	106.5	$1.07x10^{-4}$	$1.07x10^{-4}$
Logistic	2.16	1.61	0.929	104.7	$1.97x10^{-1}$	$1.97x10^{-1}$
Log-Probit	3.73	2.56	0.964	106.5	$1.63x10^{-3}$	$-2.51x10^{-4}$
Probit[g]	**1.91**	**1.46**	**0.988**	**104.6**	**$7.35x10^{-2}$**	**$7.35x10^{-2}$**

[a]BMC and BMCL 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 for dose group near the BMC and for the control dose group.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]Recommended model. Among models providing adequate fit to the data, $BMCL_{10}$ values varied by <3-fold; therefore, the model with the lowest AIC was selected as the best-fitting model (Probit).

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); NA = not applicable

Model predictions for combined incidences of olfactory epithelium metaplasia in the male and female mice are presented in Table A-14. The LogLogistic model was the only model to provide adequate fit to the data (goodness-of-fit p-value >0.1). The $BMCL_{10}$ of 1.96 ppm was selected as a potential POD.

Table A-14. Model Predictions for Olfactory Epithelium Metaplasia in Male and Female B6C3F1/N Mice Exposed to 1,1-Dichloroethene for 6 Hours/Day, 5 Days/Week for 105 Weeks (NTP 2015a)

Model	BMC_{10}[a] (ppm)	$BMCL_{10}$[a] (ppm)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose near BMC	Control group
Dichotomous Hill			NA	271.52	-1.16×10^{-7}	-1.87×10^{-7}
Gamma[d]			0.0139	273.66	4.38×10^{-2}	4.38×10^{-2}
Log-Logistic[e,f]	**2.95**	**1.96**	**0.2450**	**270.62**	**1.62×10^{-2}**	**1.62×10^{-2}**
Multistage Degree 3[g]			0.0133	275.24	1.13×10^{-1}	1.13×10^{-1}
Multistage Degree 2[g]			0.0134	275.24	1.13×10^{-1}	1.13×10^{-1}
Multistage Degree 1[g]			0.0553	274.05	2.12×10^{-1}	2.12×10^{-1}
Weibull[d]			0.0149	274.34	7.88×10^{-2}	7.88×10^{-2}
Logistic			0.0024	271.95	-1.58×10^{-1}	-1.58×10^{-1}
Log-Probit			0.0742	271.99	3.37×10^{-2}	3.37×10^{-2}
Probit			<0.0001	278.41	-7.91×10^{-1}	-7.91×10^{-1}

[a]BMC and BMCL values for models that do not provide adequate are not included in this table.
[b]Values <0.1 fail to meet adequate fit.
[c]Scaled residuals for dose group near the BMC and for the control dose group.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Recommended model. Log-Logistic is the only model which provided adequate fit.
[g]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); NA = not applicable

Table A-15 summarizes the BMC_{10} and $BMCL_{10}$ values for the nasal lesion incidences in the male and female mice exposed to 1,1-dichloroethene for 6 hours/day, 5 days/week for 105 weeks (NTP 2015a). The BMC_{10} of 1.91 ppm for olfactory epithelium metaplasia in the female mice was selected because it represents the lowest BMC_{10} among the best-fitting models for nasal lesions. The corresponding $BMCL_{10}$ of 1.46 ppm serves as the POD for deriving a chronic-duration inhalation MRL for 1,1-dichloroethene. The Probit model for olfactory epithelial metaplasia in female mice is presented in Figure A-2.

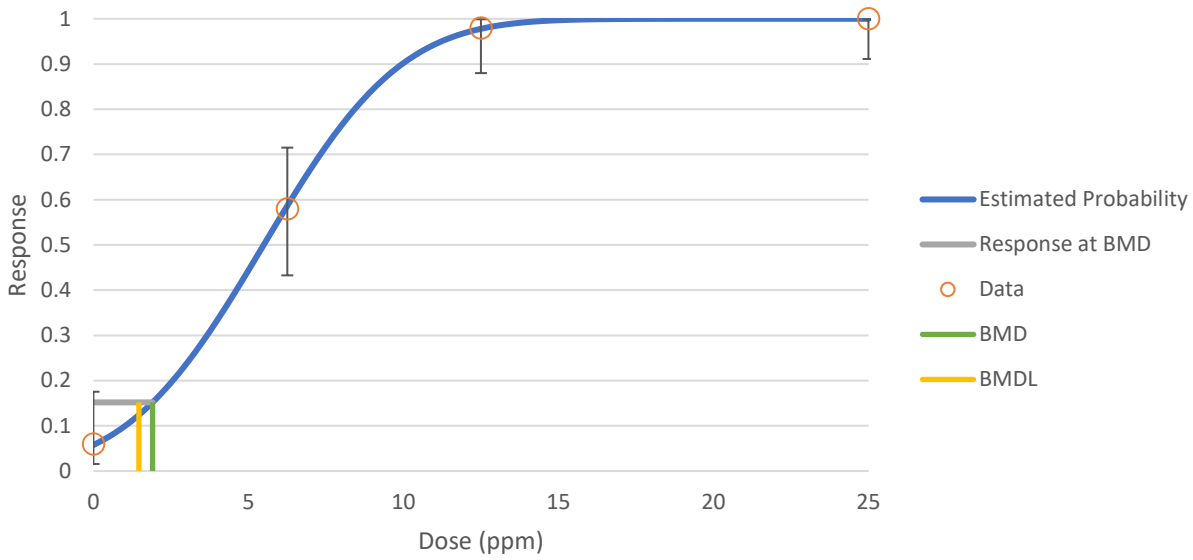
Table A-15. BMC_{10} and $BMCL_{10}$ Values from the Best-Fitting Models for Selected Nonneoplastic Nasal Lesions in B6C3F1/N Mice Exposed to 1,1-Dichloroethene Vapor 6 Hours/Day, 5 Days/Week for 105 Weeks

Lesion type	Sex	Model	BMC_{10} (ppm)	$BMCL_{10}$ (ppm)
Turbinate Hyperostosis	Male	Log-Logistic	2.84	1.66
	Female	NA		
	Combined	NA		
Olfactory epithelium Metaplasia	Male	NA		
	Female	**Probit**	**1.91**	**1.46[a]**
	Combined	Log-Logistic	2.95	1.96

[a]The $BMCL_{10}$ of 1.46 ppm for olfactory epithelial metaplasia in female mice was selected as the preferred POD for deriving a chronic-duration inhalation MRL for 1,1-dichloroethene because it corresponds to the lowest BMC_{10} (1.91 ppm) among the group of best-fitting models for nasal lesions.

BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); MRL = minimum risk level; NA = not applicable (no model provided adequate fit to the data); POD = point of departure

Figure A-2. Fit of Probit Model for Olfactory Epithelial Metaplasia Female B6C3F1/N Mice Exposed to 1,1-Dichloroethene 6 Hours/Day, 5 Days/Week for 105 Weeks



Intermittent Exposure: The $BMCL_{10}$ of 1.46 ppm was adjusted from intermittent exposure to a continuous exposure scenario according to the following equation:

$BMCL_{ADJ}$ = $BMCL_{10}$ (1.46 ppm) x 6 hours/24 hours x 5 days/7 days = 0.261 ppm

Human Equivalent Concentration: To calculate a HEC, the $BMCL_{ADJ}$ was multiplied by the regional gas dose ratio (mouse:human) for $RGDR_{ET}$. The $RGDR_{ET}$ was calculated according to the EPA (1994) equation 4-18:

$$RGDR_{ET} = \frac{\left(\frac{V_E}{SA_{ET}}\right)A}{\left(\frac{V_E}{SA_{ET}}\right)H}$$

where:
ET = extrathoracic region
V_E = minute volume (mL/minute)
SA = surface area (cm^2)
A = animal (mouse)
H = human

SA_{ET} values for the mouse (3 cm^2) and humans (200 cm^2) were taken from Table 4-4 of EPA (1994). The chronic minute volume (V_E) for the male B6C3F1 mouse was taken from Table 1-4 of EPA (1988b) in which it was presented as 0.060 m^3/day (41.67 mL/minute). According to EPA (1994), the default minute volume for humans is 13,800 mL/minute. Therefore:

$$RGDR_{ET} = \frac{\left(\frac{V_E}{SA_{ET}}\right)A}{\left(\frac{V_E}{SA_{ET}}\right)H} = \frac{\frac{41.67\ mL/min}{3\ cm^2}}{\frac{13{,}800\ mL/min}{200\ cm^2}} = 0.20$$

The $BMCL_{HEC}$ = $BMCL_{ADJ}$ x $RGDR_{ET}$ = 0.261 ppm x 0.20 = 0.052 ppm

Uncertainty Factor: The $BMCL_{HEC}$ of 0.052 ppm was divided by a total uncertainty factor of 30:

- 3 for extrapolation from animals to humans using dosimetric adjustment
- 10 for human variability

MRL = $BMCL_{HEC}$ ÷ UFs
0.028 ppm ÷ (3 x 10) = 0.0017 ppm ≈0.002 ppm

This MRL is slightly higher than the intermediate-duration inhalation MRL of 0.001 ppm. Thus, the intermediate-duration inhalation MRL based on increased incidences of necrosis of the nasal olfactory epithelium in male rats was adopted as the chronic MRL.

Other Additional Studies or Pertinent Information that Lend Support to this MRL: The nasal cavity was among the most sensitive targets of toxicity in male and female F344/N rats and B6C3F1/N mice intermittently exposed to 1,1-dichloroethene vapor for 14 or 105 weeks (NTP 2015a).

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,1-Dichloroethene
CAS Numbers: 75-35-4
Date: April 2022
Profile Status: Final
Route: Oral
Duration: Acute

MRL Summary: Available data were not considered adequate for derivation of an acute-duration oral MRL for 1,1-dichloroethene.

Rationale for Not Deriving an MRL: No dose-response data are available for humans. Many acute-duration studies employed fasted animals which are known to be more sensitive than nonfasted rats to 1,1-dichloroethene-induced adverse effects following oral exposure. The increased sensitivity to 1,1-dichloroethene in fasted animals appears to be related to toxicokinetic parameters. Levels of radioactivity in liver, kidneys, and lungs of fasted rats treated with ^{14}C-1,1-dichloroethene were significantly greater than levels in nonfasted rats (McKenna et al. 1978a). 1,1-Dichloroethene-induced hepatic lesions appeared earlier and were more extensive in fasted rats compared to nonfasted rats (Jaeger et al. 1974; McKenna et al. 1978b; Reynolds and Moslen 1977). Liver mixed function oxidase activity in fasted animals following 1,1-dichloroethene exposure was greater than that in similarly treated nonfasted animals (McKenna et al. 1978b; Nakajima et al. 1982). Due to increased sensitivity to 1,1-dichloroethene toxicity among fasted animals, only oral data from nonfasted animals (i.e., normal diet) were considered for MRL derivation. Some studies did not provide dose-response data because only a single dose level was used. Table A-16 summarizes available results from acute-duration oral studies in laboratory animals. Among studies that employed multiple dose levels and nonfasted animals, the lowest LOAEL is 100 mg/kg/day for 11% depressed body weight in female rats administered 1,1-dichloroethene by gavage for 14 days (NTP 1982). Given the limited database of information for the gavage exposure route and no information regarding the effects of acute-duration dietary or drinking water exposure, it is not considered appropriate to derive an acute-duration oral MRL for 1,1-dichloroethene at this time.

Table A-16. Summary of Potential Candidate Critical Effects for Deriving an Acute-Duration Oral MRL for 1,1-Dichloroethene

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Body weight effects					
F344/N rat	14 days 1 time/day (GO)	100 M 50 F	500 M 100 F	Depressed body weight	NTP 1982
Respiratory effects					
C57BL/6 male mouse	Once (GO)	ND	100	Reversible cellular changes in Clara cells (club cells) of bronchiolar epithelium	Forkert and Reynolds 1982
Hepatic effects					
F344/N rat	14 days 1 time/day (GO)	500 M 250 F	1,000 M 500 F	Liver necrosis at lethal dose levels	NTP 1982

Table A-16. Summary of Potential Candidate Critical Effects for Deriving an Acute-Duration Oral MRL for 1,1-Dichloroethene

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
B6C3F1 mouse	14 days 1 time/day (GO)	100	500	Liver necrosis at lethal dose level	NTP 1982

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

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,1-Dichloroethene
CAS Numbers: 75-35-4
Date: April 2022
Profile Status: Final
Route: Oral
Duration: Intermediate

MRL Summary: Available data were not considered adequate for derivation of an intermediate-duration oral MRL for 1,1-dichloroethene.

Rationale for Not Deriving an MRL: No dose-response data are available for humans. Table A-17 summarizes potential candidate critical effect PODs from intermediate-duration oral studies in laboratory animals. The 90-day gavage studies of rats and mice (NTP 1982) were the only available intermediate-duration oral studies in which treatment-related adverse effects were observed. Given the limited database of information for the gavage exposure route and no information regarding the effects of intermediate-duration dietary or drinking water exposure, it is not considered appropriate to derive an intermediate-duration oral MRL for 1,1-dichloroethene at this time.

Table A-17. Summary of Potential Candidate Critical Effects for Deriving an Intermediate-Duration Oral MRL for 1,1-Dichloroethene

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
F344/N rat	90 days 5 days/week 1 time/day (GO)	40	100	Hepatocytomegaly in males; fibrosis, pigmentation, bile duct hyperplasia in females	NTP 1982
B6C3F1 mouse	90 days 5 days/week 1 time/day (GO)	40	100	Liver necrosis and other cellular changes at lethal dose level	NTP 1982

GO = gavage in oil; LOAEL = lowest observed adverse effect level; NOAEL = no-observed-adverse-effect level

Agency Contacts (Chemical Managers): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,1-Dichloroethene
CAS Numbers: 75-35-4
Date: April 2022
Profile Status: Final
Route: Oral
Duration: Chronic
MRL 0.05 mg/kg/day
Critical Effect: Hepatic midzonal fatty change
References: Humiston et al. 1978; Quast et al. 1983
Point of Departure: $BMDL_{10}$ of 4.51 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 28
Species: Rat

MRL Summary: A MRL of 0.05 mg/kg/day has been derived for chronic-duration oral exposure to 1,1-dichloroethene based on hepatic effects (hepatic midzonal fatty change) in female Sprague-Dawley rats receiving 1,1-dichloroethene from the drinking water for up to 2 years (Humiston et al. 1978; Quast et al. 1983). The MRL is based on a $BMDL_{10}$ of 4.51 mg/kg/day and divided by a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Selection of the Critical Effect: No dose-response human data are available. Relatively limited data are available regarding the effects of chronic-duration oral exposure of animals to 1,1-dichloroethene. Two groups of investigators found no evidence of 1,1-dichloroethene toxicity at the highest dose levels tested, although these doses were ≤20 mg/kg/day (Maltoni et al. 1985; NTP 1982). A single 2-year drinking water study reported increased incidences of hepatocellular hypertrophy and midzonal fatty changes (the only reported adverse effect) in male and female rats at estimated 1,1-dichloroethene doses of 20 and 9 mg/kg/day, respectively (Humiston et al. 1978; Quast et al. 1983). A NOAEL of 10 mg/kg/day was identified for the male rats; the LOAEL of 9 mg/kg/day for the female rats was the lowest dose tested.

Selection of the Principal Studies: The 2-year rat study (Humiston et al. 1978; Quast et al. 1983) was selected as the principal study for deriving a chronic-duration oral MRL for 1,1-dichloroethene because it identified the lowest LOAEL (9 mg/kg/day) for nonneoplastic effects.

Summary of the Principal Studies:

Humiston CG, Quast JF, Wade CE, et al. 1978. Results of a two-year toxicity and oncogenicity study with vinylidene chloride incorporated in the drinking water of rats. Toxicology Research Laboratory, Health and Environmental Research, Dow Chemical USA. Chem Mfgs Assn. Submitted to the U.S. EPA under TSCA section FYI.

Quast JF, Humiston CG, Wade CE, et al. 1983. A chronic toxicity and oncogenicity study in rats and subchronic toxicity study in dogs on ingested vinylidene chloride. Fundam Appl Toxicol 3(1):55-62.

In the principal study, groups of Sprague-Dawley rats (48/sex/group; 80/sex for controls; 6–7 weeks of age) were administered 1,1-dichloroethene in the drinking water for 2 years at 50, 100, or 200 ppm (author-estimated doses of 7, 10, and 20 mg/kg/day, respectively, for males, and 9, 14, and 30 mg/kg/day, respectively, for females). Controls consisted of 80 rats/sex that received drinking water without 1,1-dichloroethene. Rats were monitored for survival, clinical signs, body weight, and food intake. Blood and urine were collected from at least five rats/sex/group at 6, 12, 18, and 23 months for

hematology and urinalysis. Clinical chemistry evaluations were performed on 5 rats/sex/group at 6, 12, and 18 months, and from all surviving rats from each group in which <10 rats remained at terminal sacrifice. At sacrifice, weights of brain, heart, liver, kidneys, and testes were recorded. Comprehensive gross pathological examinations were performed on all rats. Comprehensive histopathologic examinations were performed on control and high-dose rats; histopathology was also performed on selected target organs and grossly recognized neoplastic changes in low- and mid-dose rats.

There were no significant treatment-related differences from controls in appearance and demeanor, mortality, body weight, food consumption, water consumption, hematology, urinalysis, clinical chemistry, or organ weight. The sole treatment-related observation was microscopic changes in the liver (minimal amount of hepatocellular swelling with midzonal fatty change). The incidences of midzonal fatty change in the controls, low-, mid-, and high-dose rats are presented in Table A-18. Incidences of midzonal fatty change were significantly increased in the high-dose males (20 mg/kg/day) and mid- (14 mg/kg/day) and high-dose (30 mg/kg/day) females. Incidences of minimal hepatocellular swelling, summarized in Table A-18, were significantly increased in females at all 1,1-dichloroethene dose levels. The mid-dose (10 mg/kg/day) and high-dose (20 mg/kg/day) are considered male rat NOAEL and LOAEL levels, respectively, for histopathologic liver effects. The low-dose (9 mg/kg/day) is considered a minimum LOAEL for the female rat, based on the minimal nature of hepatocellular swelling at that dose level.

Table A-18. Incidence Data for Selected Nonneoplastic Liver Lesions in Male and Female Sprague-Dawley Rats Administered 1,1-Dichloroethene in the Drinking Water for up to 2 Years[a]

Lesion type				
Males				
Time-weighted average dose (mg/kg/day)	0	7	10	20
Minimal hepatocellular hypertrophy	0/76	0/46	1/45	3/42[b]
Minimal midzonal fatty change	12/76	4/46	13/45	18/42[c]
Females				
Time-weighted average dose (mg/kg/day)	0	9	14	30
Minimal hepatocellular hypertrophy	3/79	7/48[b]	11/45[c]	20/48[c]
Minimal midzonal fatty change	10/79	12/48	14/45[b]	22/48[c]

[a]Incidence in animals dying or killed between 13 and 24 months.
[b]Significantly different from control incidence according to Fisher's exact test ($p<0.05$).
[c]Significantly different from control incidence according to Fisher's exact test ($p<0.01$).

Sources: Humiston et al. 1978; Quast et al. 1983

Selection of the Point of Departure for the MRL: A $BMDL_{10}$ of 4.51 mg/kg/day for hepatic midzonal fatty changes in female rats estimated using the frequentist-restricted Gamma model was selected as the POD for the chronic-duration oral MRL for 1,1-dichloroethene.

The lowest LOAEL identified in the 2-year rat study (Humiston et al. 1978; Quast et al. 1983) was 9 mg/kg/day for increased hepatocellular hypertrophy in female rats. Incidence data for these effects are presented in Table A-18.

The incidence data for hepatocellular hypertrophy and for midzonal fatty change in the female rats were fit to all standard dichotomous models in EPA's BMDS (version 3.1.2) using a BMR of 10% change in incidence from controls. Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), scaled residuals (within ±2 units) at the data points (except the control) closest to the predefined BMR, BMDL that was not 10 times lower than the lowest non-zero dose, and visual inspection of the proximity of the predicted dose-response curve to the observed data points closest to the BMR. For each dataset, among all 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 model predictions for hepatocellular hypertrophy are presented in Table A-19. Most models provided adequate fit to the data; the dichotomous Hill model because the goodness of fit test could not be calculated. BMDLs for models providing adequate fit differed by <3-fold; therefore, the model with the lowest AIC (1-degree Multistage) was selected as a potential POD.

Table A-19. Model Predictions for Hepatocellular Hypertrophy in Female Sprague-Dawley Rats Receiving 1,1-Dichloroethene from the Drinking Water for 2 Years (Humiston et al. 1978; Quast et al. 1983)

Model	BMD_{10}[a] (mg/kg/day)	$BMDL_{10}$[a] (mg/kg/day)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose near BMD	Control group
Dichotomous Hill			NA	188.65	-2.41×10^{-5}	3.01×10^{-6}
Gamma[d]	7.33	4.82	0.711	186.78	-2.21×10^{-1}	1.30×10^{-2}
Log-Logistic[e]	7.52	4.13	0.747	186.75	-1.94×10^{-1}	1.40×10^{-2}
Multistage Degree 3[f]	7.02	4.81	0.685	186.81	-2.72×10^{-1}	2.38×10^{-2}
Multistage Degree 2[f]	7.02	4.81	0.685	186.81	-2.73×10^{-1}	2.47×10^{-2}
Multistage Degree 1[f,g]	6.46	4.79	0.897	184.87	-4.10×10^{-1}	7.14×10^{-2}
Weibull[d]	7.27	4.81	0.706	186.79	-2.32×10^{-1}	1.51×10^{-2}
Logistic	12.12	10.06	0.276	187.28	1.12	-9.81×10^{-1}
Log-Probit[g]	**7.79**	**2.66**	**0.793**	**186.71**	$\mathbf{-1.51 \times 10^{-1}}$	$\mathbf{1.17 \times 10^{-2}}$
Probit	11.25	9.33	0.372	186.64	3.48×10^{-1}	-7.95×10^{-1}

[a]BMD and BMDL 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 for dose group near the BMD and for the control dose group.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]Recommended model. Most models provided adequate fit to the data. BMDLs differed by >3-fold; therefore, the models with the lowest BMDL (Log-Probit) was selected as best-fitting model.

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., $_{10}$ = exposure dose associated with 10% extra risk); NA = not applicable

The model predictions for midzonal fatty change are presented in Table A-20. The Dichotomous Hill model and Log-Probit models did not provide adequate to the data (saturated model and BMDL 10 times lower than lowest non-zero dose, respectively). The BMDLs for the models providing adequate fit differed by <3-fold; therefore, the model with the lowest AIC was selected (Gamma) and the $BMDL_{10}$ was considered a potential POD.

Table A-20. Model Predictions for Hepatic Midzonal Fatty Change in Female Sprague-Dawley Rats Receiving 1,1-Dichloroethene from the Drinking Water for 2 Years (Humiston et al. 1978; Quast et al. 1983)

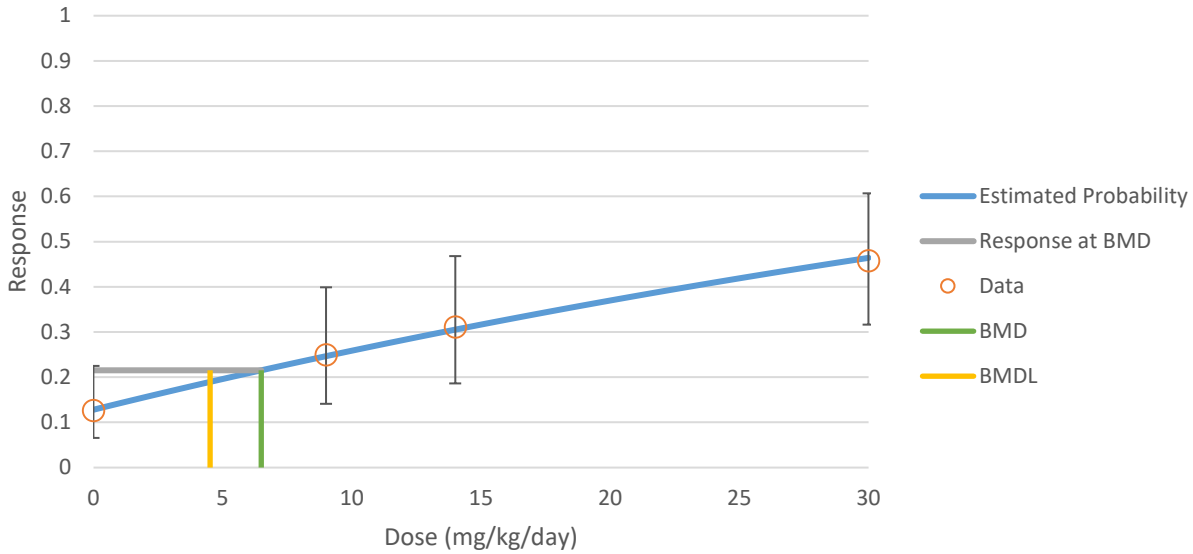
Model	BMD_{10}[a] (mg/kg/day)	$BMDL_{10}$[a] (mg/kg/day)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose near BMD	Control group
Dichotomous Hill			NA	244.01	-3.64×10^{-3}	3.77×10^{-4}
Gamma[d,e]	**6.49**	**4.51**	**0.991**	**240.02**	**5.52×10^{-2}**	**-3.99×10^{-2}**
Log-Logistic[f]	6.26	3.64	0.994	242.01	-4.81×10^{-3}	3.82×10^{-4}
Multistage Degree 3[g]	6.49	4.51	0.991	240.02	5.52×10^{-3}	-3.99×10^{-2}
Multistage Degree 2[g]	6.49	4.51	0.991	240.02	5.52×10^{-2}	-3.99×10^{-2}
Multistage Degree 1[g]	6.49	4.51	0.991	240.02	5.52×10^{-2}	-3.99×10^{-2}
Weibull[d]	6.49	4.51	0.991	240.02	5.52×10^{-2}	-3.99×10^{-2}
Logistic	10.02	7.97	0.645	240.89	4.38×10^{-1}	-5.48×10^{-1}
Log-Probit			0.978	242.01	1.59×10^{-2}	-1.50×10^{-3}
Probit	9.53	7.55	0.698	240.72	4.08×10^{-1}	-4.71×10^{-1}

[a]BMD and BMDL 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 for dose group near the BMD and for the control dose group.
[d]Power restricted to ≥1.
[e]Recommended model. Most models provided adequate fit to the data. BMDLs differed by <3-fold; therefore, the models with the lowest AIC (Gamma) was selected as best-fitting model.
[f]Slope restricted to ≥1.
[g]Betas restricted to ≥0.

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., $_{10}$ = exposure dose associated with 10% extra risk); NA = not applicable

From the best-fitting models, a BMD_{10} of 7.79 mg/kg/day for hepatocellular hypertrophy (Log-Probit model Table A-19) and a BMD_{10} of 6.49 mg/kg/day for midzonal fatty change (Gamma model, Table A-20) were estimated. The $BMDL_{10}$ of 4.51 mg/kg/day for midzonal fatty change in the female rats was selected as the POD for the MRL because it had the lowest BMD_{10}. The fit of the Gamma model to the midzonal fatty changes incidence data is presented in Figure A-3.

Figure A-3. Fit Gamma Model for Hepatic Midzonal Fatty Change in Female Sprague-Dawley Rats Receiving 1,1-Dichloroethene from the Drinking Water for 2 Years



Uncertainty Factor: The $BMDL_{10}$ of 4.51 mg/kg/day was divided by a total uncertainty factor of 100:

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

$MRL = BMDL_{10} \div UFs$
$MRL = 4.51 \text{ mg/kg/day} \div (10 \times 10) = 0.045 \text{ mg/kg/day} \approx 0.05 \text{ mg/kg/day}$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Support is limited to similar findings in the male rats of the principal study, albeit at a higher dose level (20 mg/kg/day) than the LOAEL of 9 mg/kg/day observed in the female rats.

Agency Contacts (Chemical Managers): Malcolm Williams

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

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen was conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for 1,1-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 1,1-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 1,1-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 1,1-dichloroethene released for public comment in 2019; thus, the literature search was restricted to studies published between December 2015 and March 2020. The following main databases were searched in March 2020:

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

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for 1,1-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 1,1-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	
03/2020	((75-35-4[rn] OR "vinylidene chloride"[nm] OR "1,1-Dce"[tw] OR "1,1-Dichloroethene"[tw] OR "1,1-Dichloroethylene"[tw] OR "as-Dichloroethylene"[tw] OR "asym-Dichloroethylene"[tw] OR "Vinylidene chloride"[tw] OR "Vinylidene dichloride"[tw] OR "Vinylidine chloride"[tw]) AND (2016/12/01 : 3000[mhda] OR 2016/12/01 : 3000[crdt] OR 2016/12/01 : 3000[edat] OR 2015/12/01 : 3000[dp])) OR ((("1,1"[tw] AND (dichloroethene[tw] OR dce[tw] OR Dichloroethylene[tw])) AND (2016/12/01 : 3000[mhda] OR 2016/12/01 : 3000[crdt] OR 2016/12/01 : 3000[edat] OR 2015/12/01 : 3000[dp])) NOT medline[sb]) OR ("1,1-Dichlorethylene"[tw] OR "Dichloroethylene, 1,1-"[tw] OR "Diofan A 565S"[tw] OR "Ethene, 1,1-dichloro-"[tw] OR "Ethylene, 1,1-dichloro-"[tw] OR "F 1130a"[tw] OR "HCC 1130a"[tw] OR "Iso-dichloroethylene"[tw] OR "R 1130a"[tw])
NTRL	
03/2020	"1,1-Dce" OR "1,1-Dichloroethene" OR "1,1-Dichloroethylene" OR "as-Dichloroethylene" OR "asym-Dichloroethylene" OR "Vinylidene chloride" OR "Vinylidene dichloride" OR "Vinylidine chloride" OR "1,1-Dichlorethylene" OR "Dichloroethylene, 1,1-" OR "Diofan A 565S" OR "Ethene, 1,1-dichloro-" OR "Ethylene, 1,1-dichloro-" OR "F 1130a" OR "HCC 1130a" OR "Iso-dichloroethylene" OR "R 1130a" ("1,1" AND (dichloroethene OR dce OR Dichloroethylene)) "1,1-Dichlorethylene" OR "Dichloroethylene, 1,1-" OR "Diofan A 565S" OR "Ethene, 1,1-dichloro-" OR "Ethylene, 1,1-dichloro-" OR "F 1130a" OR "HCC 1130a" OR "Iso-dichloroethylene" OR "R 1130a"
Toxcenter	
03/2020	FILE 'TOXCENTER' ENTERED AT 16:46:45 ON 27 MAR 2020 CHARGED TO COST=EH038.06.01.LB.02 L1 3835 SEA FILE=TOXCENTER 75-35-4 L2 156 SEA FILE=TOXCENTER L1 AND ED>=20161201 L4 186 SEA FILE=TOXCENTER L1 AND PY>2015 L5 205 SEA FILE=TOXCENTER L2 OR L4 L6 205 SEA FILE=TOXCENTER L5 NOT TSCATS/FS L7 143 SEA FILE=TOXCENTER L6 NOT PATENT/DT ACT TOXQUERY/Q --------- L8 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L9 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT,

Table B-2. Database Query Strings

Database search date	Query string
	IT)
	L10 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50)
	L11 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT
	L12 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?)
	L13 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)
	L14 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?)
	L15 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE))
	L16 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)
	L17 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)
	L18 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
	L19 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
	L20 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L21 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L22 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L23 QUE (ENDOCRIN? AND DISRUPT?)
	L24 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L25 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L26 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L27 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L28 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L29 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L30 QUE (NEPHROTOX? OR HEPATOTOX?)
	L31 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L32 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L33 QUE 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 OR L32
	L34 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?)

Table B-2. Database Query Strings

Database search date	Query string
	L35 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE) L36 QUE L33 OR L34 OR L35 L37 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) L38 QUE L36 OR L37 --------- L39 54 SEA FILE=TOXCENTER L7 AND L38 L40 89 SEA FILE=TOXCENTER L7 NOT L39 L41 4 SEA FILE=TOXCENTER L39 AND MEDLINE/FS L43 50 SEA FILE=TOXCENTER L39 NOT MEDLINE/FS L44 52 DUP REM L41 L43 (2 DUPLICATES REMOVED) ANSWERS '1-52' FROM FILE TOXCENTER L*** DEL 4 S L39 AND MEDLINE/FS L*** DEL 4 S L39 AND MEDLINE/FS L45 4 SEA FILE=TOXCENTER L44 L*** DEL 50 S L39 NOT MEDLINE/FS L*** DEL 50 S L39 NOT MEDLINE/FS L46 48 SEA FILE=TOXCENTER L44 L47 48 SEA FILE=TOXCENTER (L45 OR L46) NOT MEDLINE/FS D SCAN L47

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
03/2020	Compounds searched: 75-35-4
NTP	
03/2020	75-35-4 "1,1-Dichloroethene" "1,1-Dichloroethylene" "Vinylidene chloride" "Vinylidine chloride" "1,1-Dce" "1,1-Dichloro-ethene" "1,1-Dichloro-ethylene" "1,1-Dichlorethylene" "Iso-dichloroethylene"
NIH RePORTER	
04/2020	Search Criteria: Text Search: "1,1-Dce" OR "1,1-Dichloroethene" OR "1,1-Dichloroethylene" OR "as-Dichloroethylene" OR "asym-Dichloroethylene" OR "Vinylidene chloride" OR "Vinylidene dichloride" OR "Vinylidine chloride" OR "1,1-Dichlorethylene" OR "Dichloroethylene, 1,1-" OR "Diofan A 565S" OR "Ethene, 1,1-dichloro-" OR "Ethylene, 1,1-dichloro-" OR "F 1130a" OR "HCC 1130a" OR "Iso-dichloroethylene" OR "R 1130a" (Advanced), Search in: Projects AdminIC: All, Fiscal Year: Active Projects
Other	Identified throughout the assessment process

The 2020 results were:

- Number of records identified from PubMed, NTRL, and TOXCENTER (after duplicate removal): 102
- Number of records identified from other strategies: 48
- Total number of records to undergo literature screening: 150

B.1.2 Literature Screening

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

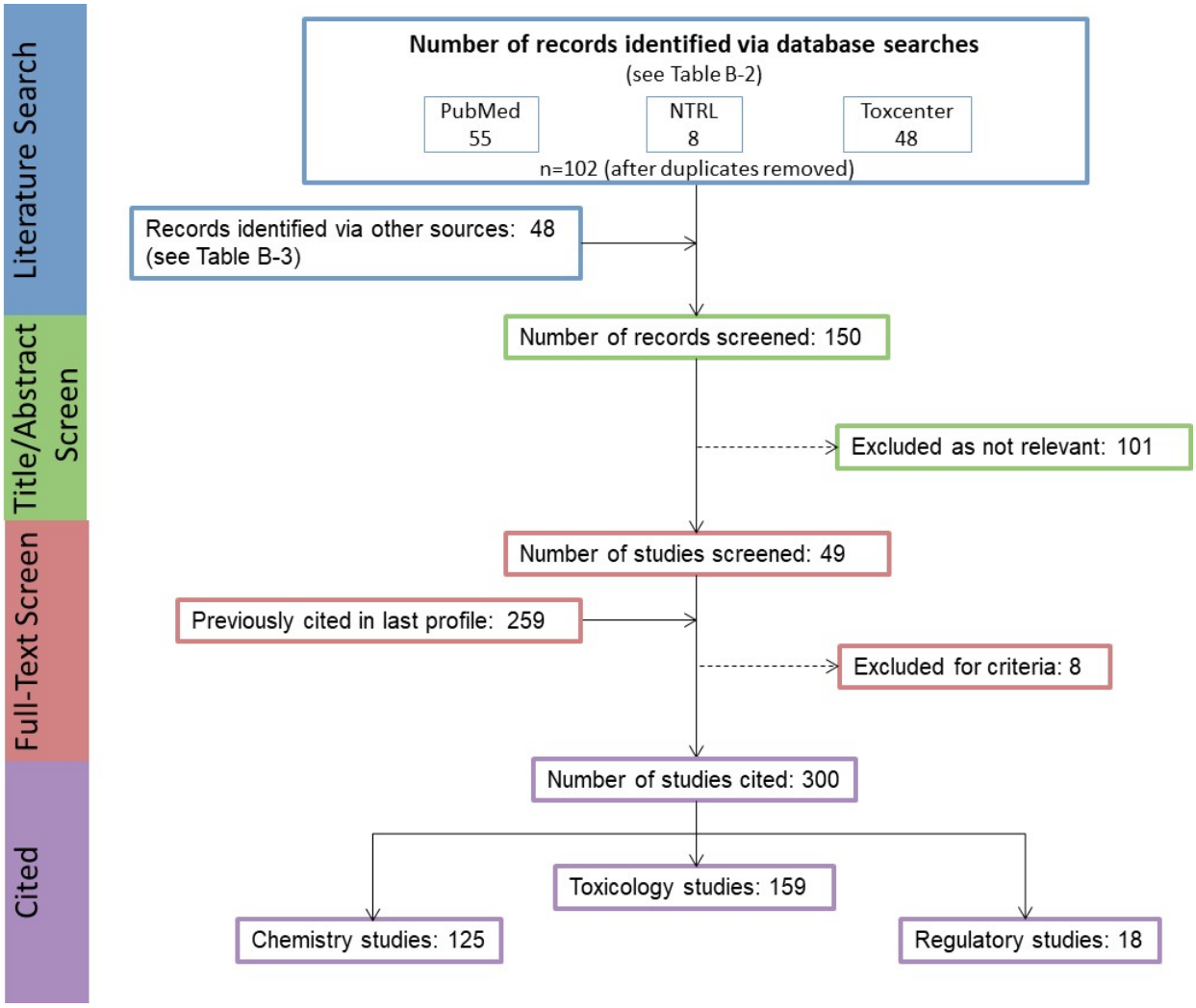
- Number of titles and abstracts screened: 150
- Number of studies considered relevant and moved to the next step: 49

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: 49
- Number of studies cited in the pre-public draft of the toxicological profile: 259
- Total number of studies cited in the profile: 300

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

Figure B-1. March 2020 Literature Search Results and Screen for 1,1-Dichloroethene



APPENDIX C. FRAMEWORK FOR ATSDR'S SYSTEMATIC REVIEW OF HEALTH EFFECTS DATA FOR 1,1-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 1,1-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 1,1-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 1,1-dichloroethene. The inclusion criteria used to identify relevant studies examining the health effects of 1,1-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 was conducted to identify studies examining the health effects of 1,1-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 draft toxicological profile for 1,1-dichloroethene released for public comment in 2019. See Appendix B for the databases searched and the search strategy.

A total of 149 records relevant to all sections of the toxicological profile were identified (after duplicate removal).

C.2.2 Literature Screening

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

Title and Abstract Screen. In the Title and Abstract Screen step, 150 records were reviewed; 0 documents were considered to meet the health effects inclusion criteria in Table C-1.

Full Text Screen. In the second step in the literature screening process for the systematic review, a full text review of 50 health effect documents (documents identified in the update literature search and documents cited in older versions of the profile) was performed. From those 50 documents, 90 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 1,1-Dichlorethene and overviews of the results of the inhalation and oral 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 and 2-2, respectively).

C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

Overviews of the potential health effect outcomes for 1,1-dichloroethene identified in human and animal studies are presented in Tables C-3 and C-4, respectively. Human studies have evaluated a limited number of endpoints (hematological, hepatic, renal, and developmental. Animal studies have examined a number of endpoints including body weight, respiratory, cardiovascular, hematological, hepatic, renal, neurological, reproductive, developmental, and cancer. These data suggest that respiratory, hepatic, and renal effects are the most sensitive outcomes. Studies examining these potential outcomes were carried through to Steps 4–8 of the systematic review. There were 90 studies (published in 50 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 1,1-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					1 0		1 0	1 0									
Case control																	
Population																	
Case series																	
Oral studies																	
Cohort																	
Case control																	
Population															1 0		
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

Table C-4. Overview of the Health Outcomes for 1,1-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	12	4	1	0	0	0	17	9	0	0	0	0	1	1	6	0	0
	6	1	1	0	0	0	13	8	0	0	0	0	1	0	4	0	0
Intermediate-duration	6	9	0	0	1	0	15	7	0	0	0	0	0	3	0	0	0
	3	4	0	0	0	0	14	4	0	0	0	0	0	2	0	0	0
Chronic-duration	8	8	0	0	3	0	10	8	0	0	1	0	0	0	0	0	4
	1	3	0	0	0	0	4	3	0	0	1	0	0	0	0	0	4
Oral studies																	
Acute-duration	3	3	1	1	1	0	11	4	0	0	0	0	0	0	1	0	0
	2	2	0	1	1	0	10	4	0	0	0	0	0	0	0	0	0
Intermediate-duration	3	0	0	0	1	0	3	1	0	0	0	0	0	0	0	0	0
	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Chronic-duration	4	4	2	1	1	0	5	5	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Dermal studies																	
Acute-duration	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Intermediate-duration	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Chronic-duration	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

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

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

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 2015b). The risk of bias questions for observational epidemiology studies, human-controlled exposure studies, and animal experimental studies are presented in Tables C-5, C-6, and C-7, respectively. Each risk of bias question was answered on a four-point scale:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

	Risk of bias criteria and ratings						
	Selection bias	Confounding bias	Attrition / exclusion bias	Detection bias		Selective reporting bias	
Reference	Comparison groups appropriate?	**Study design or analysis account for important confounding and modifying variables?***	Outcome data complete without attrition or exclusion from analysis?	**Confidence in the exposure characterization?***	**Confidence in the outcome assessment?***	All measured outcomes reported?	Risk of bias tier
Outcome: Hepatic effects							
Inhalation–cohort							
Ott et al. 1976	++	+	+	+	+	+	First
Outcome: Renal effects							
Oral–cross-sectional							
Ott et al. 1976	++	+	+	+	+	+	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

Table C-9. Summary of Risk of Bias Assessment for 1,1-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	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	Study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Outcome: Respiratory effects										
Inhalation acute exposure										
Henck et al. 1979 (mouse; Ha[ICR])	+	+	++	+	+	++	++	+	na	First
Henck et al. 1979 (mouse; B6C3F1)	+	+	++	+	+	++	++	+	na	First
Henck et al. 1979 (mouse; CD-1)	+	+	++	+	+	++	++	+	na	First
Henck et al. 1979 (mouse; CF-W)	+	+	++	+	+	++	++	+	na	First
Zeller et al. 1979a (rat)	+	+	+	+	+	+	+	+	na	First
Oral acute exposure										
Chieco et al. 1981 (rat)	+	+	+	+	+	++	++	+	na	First
Forkert and Reynolds 1982 (mouse)	+	+	+	+	+	++	++	+	na	First
Forkert et al. 1985 (mouse)	+	na	na	na	na	++	++	+	na	First
Inhalation intermediate exposure										
Gage 1970 (rat)	+	+	+	+	+	++	++	+	na	First
Maltoni et al. 1985 (rat)	+	+	+	+	+	+	+	+	na	First
NTP 2015a (rat; 14 weeks)	+	+	++	+	+	++	++	+	na	First
NTP 2015a (mouse; 17 days)	+	+	++	+	+	++	++	+	na	First
NTP 2015a (mouse 14 weeks)	+	+	++	+	+	++	++	+	na	First

Table C-9. Summary of Risk of Bias Assessment for 1,1-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	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	Study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Prendergast et al. 1967 (rat)	+	+	++	+	+	++	++	+	na	First
Prendergast et al. 1967 (guinea pig)	+	+	++	+	+	++	++	+	na	First
Prendergast et al. 1967 (dog)	+	+	++	+	+	++	++	+	na	First
Quast et al. 1986 (rat)	+	+	++	+	+	++	++	++	na	First
Inhalation chronic exposure										
Maltoni et al. 1985 (rat; 104 weeks)	+	+	+	+	+	+	+	+	na	First
Maltoni et al. 1985 (rat; 52 weeks)	+	+	+	+	+	+	+	+	na	First
Maltoni et al. 1985 (mouse; 10, 25 ppm)	+	+	+	+	+	+	+	+	na	First
Maltoni et al. 1985 (mouse; 25 ppm)	+	+	+	+	+	+	+	+	na	First
Maltoni et al. 1985 (hamster)	+	+	+	+	+	+	+	+	na	First
NTP 2015a (rat)	+	+	++	+	+	++	++	++	na	First
NTP 2015a (mouse)	+	+	++	+	+	++	++	++	na	First
Quast et al. 1986 (rat)	+	+	++	+	+	++	++	++	na	First
Oral chronic exposure										
Maltoni et al. 1985 (rat; 0.5 mg/kg/day)	+	+	+	+	+	+	+	+	na	First
Maltoni et al. 1985 (rat; 5, 10, 20 mg/kg/day)	+	+	+	+	+	+	+	+	na	First
NTP 1982 (rat)	+	+	++	+	+	++	++	++	na	First

Table C-9. Summary of Risk of Bias Assessment for 1,1-Dichloroethene—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	Study design or analysis account for important confounding and modifying variables?	
NTP 1982 (mouse)	+	+	++	+	+	++	++	++	na	First
Outcome: Hepatic effects										
Inhalation acute exposure										
Henck et al. 1979 (mouse; Ha[ICR])	+	+	++	+	+	++	++	+	na	First
Henck et al. 1979 (mouse; B6C3F1)	+	+	++	+	+	++	++	+	na	First
Henck et al. 1979 (mouse; CD-1)	+	+	++	+	+	++	++	+	na	First
Henck et al. 1979 (mouse; CF-W)	+	+	++	+	+	++	++	+	na	First
Jaeger 1977 (rat)	+	na	na	na	+	+	+	+	na	First
Jaeger et al. 1973a (rat)	+	na	na	na	+	+	+	+	na	First
Jaeger et al. 1974 (rat; fasted)	+	+	+	+	+	++	+	+	na	First
Jaeger et al. 1974 (rat; nonfasted)	+	+	+	+	+	++	+	+	na	First
Maltoni et al. 1985 (mouse)	+	+	+	+	+	+	+	+	na	First
McKenna et al. 1978a (rat)	+	+	+	+	+	++	+	+	na	First
Murray et al. 1979 (rat; 80 ppm)	+	+	+	+	+	+	+	+	na	First
Murray et al. 1979 (rat; 160 ppm)	+	+	+	+	+	+	+	+	na	First
Murray et al. 1979 (rabbit; 80 ppm)	+	+	+	+	+	+	+	+	na	First
Murray et al. 1979 (rabbit; 160 ppm)	+	+	+	+	+	+	+	+	na	First
Reitz et al. 1980 (mouse)	+	+	+	+	+	+	+	+	na	First

Table C-9. Summary of Risk of Bias Assessment for 1,1-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	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	Study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Short et al. 1977a, 1977b (rat)	+	+	+	+	+	+	+	+	na	First
Short et al. 1977a, 1977b (mouse)	+	+	+	+	+	+	+	+	na	First
Oral acute exposure										
Chieco et al. 1981 (rat; 200 mg/kg/day)	+	+	+	+	+	++	+	+	na	First
Chieco et al. 1981 (rat; 50–200 mg/kg/day)	+	+	+	+	+	++	+	+	na	First
Jaeger et al. 1973b (rat)	+	+	+	+	+	++	+	+	na	First
Jenkins and Andersen 1978 (rat)	+	+	+	+	+	++	+	+	na	First
Kanz and Reynolds 1986 (rat)	+	+	+	+	+	++	+	+	na	First
Kanz et al. 1991 (rat)	+	+	+	+	+	++	+	+	na	First
Moslen et al. 1985 (rat)	+	+	+	+	+	++	+	+	na	First
Murray et al. 1979 (rat)	+	+	+	+	+	+	+	+	na	First
NTP 1982 (rat)	+	+	+	+	+	++	+	+	na	First
NTP 1982 (mouse)	+	+	+	+	+	++	+	+	na	First
Reynolds et al. 1984 (rat)	+	+	+	+	+	++	+	+	na	First
Inhalation intermediate exposure										
Balmer et al. 1976 (rat)	+	+	+	+	+	+	+	+	na	First
Gage 1970 (rat)	+	+	+	+	+	++	++	+	na	First

Table C-9. Summary of Risk of Bias Assessment for 1,1-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	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	Study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Maltoni et al. 1985 (rat)	+	+	+	+	+	+	+	+	na	First
NTP 2015a (rat; 16 days)	+	+	++	+	+	++	++	+	na	First
NTP 2015a (rat; 14 weeks)	+	+	++	+	+	++	++	+	na	First
NTP 2015a (mouse; 17 days)	+	+	++	+	+	++	++	+	na	First
NTP 2015a (mouse; 14 weeks)	+	+	++	+	+	++	++	+	na	First
Plummer et al. 1990 (rat; continuous)	+	+	+	+	+	+	+	+	na	First
Plummer et al. 1990 (rat; intermittent)	+	+	+	+	+	+	+	+	na	First
Prendergast et al. 1967 (monkey)	+	+	++	+	+	++	++	+	na	First
Prendergast et al. 1967 (rat)	+	+	++	+	+	++	++	+	na	First
Prendergast et al. 1967 (guinea pig)	+	+	++	+	+	++	++	+	na	First
Prendergast et al. 1967 (dog)	+	+	++	+	+	++	++	+	na	First
Quast 1976 (rat)	+	+	+	+	+	+	+	+	na	First
Quast et al. 1986 (rat)	+	+	++	+	+	++	++	++	na	First
Oral intermediate exposure										
NTP 1982 (rat)	+	+	+	+	+	++	++	+	na	First
NTP 1982 (mouse)	+	+	+	+	+	++	++	+	na	First
Quast et al. 1983 (dog)	+	+	+	+	+	++	++	+	na	First

Table C-9. Summary of Risk of Bias Assessment for 1,1-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	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	Study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Inhalation chronic exposure										
Lee et al. 1977, 1978 (rat)	+	+	+	+	+	++	+	+	na	First
Lee et al. 1977, 1978 (mouse)	+	+	+	+	+	++	+	+	na	First
Maltoni et al. 1985 (rat; 104 weeks)	+	+	+	+	+	+	+	+	na	First
Maltoni et al. 1985 (rat; 52 weeks)	+	+	+	+	+	+	+	+	na	First
Maltoni et al. 1985 (mouse; 10, 25 ppm)	+	+	+	+	+	+	+	+	na	First
Maltoni et al. 1985 (mouse; 25 ppm)	+	+	+	+	+	+	+	+	na	First
Maltoni et al. 1985 (hamster)	+	+	+	+	+	+	+	+	na	First
NTP 2015a (rat; 105 weeks)	+	+	++	+	+	++	++	++	na	First
NTP 2015a (mouse; 105 weeks)	+	+	++	+	+	++	++	++	na	First
Oral chronic exposure										
Maltoni et al. 1985 (rat; 0.5 mg/kg/day)	+	+	+	+	+	+	+	+	na	First
Maltoni et al. 1985 (rat; multidose)	+	+	+	+	+	+	+	+	na	First
NTP 1982 (rat)	+	+	++	+	+	++	++	++	na	First
NTP 1982 (mouse)	+	+	++	+	+	++	++	++	na	First
Quast et al. 1983 (rat)	+	+	++	+	+	++	++	++	na	First

Table C-9. Summary of Risk of Bias Assessment for 1,1-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	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	Study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Outcome: Renal effects										
Inhalation acute exposure										
Henck et al. 1979 (mouse; Ha[ICR])	+	+	++	+	+	++	++	+	na	First
Henck et al. 1979 (mouse; B6C3F1)	+	+	++	+	+	++	++	+	na	First
Henck et al. 1979 (mouse; CD-1)	+	+	++	+	+	++	++	+	na	First
Henck et al. 1979 (mouse; CF-W)	+	+	++	+	+	++	++	+	na	First
Jackson and Conolly 1985 (rat)	+	+	++	+	+	++	++	+	na	First
Maltoni et al. 1985 (mouse)	+	+	+	+	+	+	+	+	na	First
McKenna et al. 1978a (rat)	+	+	+	+	+	++	+	+	na	First
Short et al. 1977a, 1977b (rat)	+	+	+	+	+	+	+	+	na	First
Short et al. 1977a, 1977b (mouse)	+	+	+	+	+	+	+	+	na	First
Oral acute exposure										
Chieco et al. 1981 (rat)	+	+	+	+	+	++	+	+	na	First
Jenkins and Andersen 1978 (rat; single dose)	+	+	+	+	+	++	+	+	na	First
Jenkins and Andersen 1978 (rat; multidose)	+	+	+	+	+	++	+	+	na	First

Table C-9. Summary of Risk of Bias Assessment for 1,1-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	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	Study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Jenkins and Andersen 1978 (rat; single dose)	+	+	+	+	+	++	+	+	na	First
Inhalation intermediate exposure										
Maltoni et al. 1985 (rat)	+	+	+	+	+	+	+	+	na	First
NTP 2015a (rat; 16 days)	+	+	++	+	+	++	++	+	na	First
NTP 2015a (rat; 14 weeks)	+	+	++	+	+	++	++	+	na	First
NTP 2015a (mouse; 17 days)	+	+	++	+	+	++	++	+	na	First
NTP 2015a (mouse; 14 weeks)	+	+	++	+	+	++	++	+	na	First
Prendergast et al. 1967 (rat)	+	+	++	+	+	++	++	+	na	First
Prendergast et al. 1967 (dog)	+	+	++	+	+	++	++	+	na	First
Oral intermediate exposure										
Quast et al. 1983 (dog)	+	+	+	+	+	++	++	+	na	First
Inhalation chronic exposure										
Maltoni et al. 1985 (rat; 104 weeks)	+	+	+	+	+	+	+	+	na	First
Maltoni et al. 1985 (rat; 52 weeks)	+	+	+	+	+	+	+	+	na	First
Maltoni et al. 1985 (mouse; 10, 25 ppm)	+	+	+	+	+	+	+	+	na	First
Maltoni et al. 1985 (mouse; 25 ppm)	+	+	+	+	+	+	+	+	na	First
Maltoni et al. 1985 (hamster)	+	+	+	+	+	+	+	+	na	First

Table C-9. Summary of Risk of Bias Assessment for 1,1-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	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	Study design or analysis account for important confounding and modifying variables?	Risk of bias tier
NTP 2015a (rat; 105 weeks)	+	+	++	+	+	++	++	++	na	First
NTP 2015a (mouse; 105 weeks)	+	+	++	+	+	++	++	++	na	First
Quast et al. 1986 (rat)	+	+	++	+	+	++	++	++	na	First
Oral chronic exposure										
Maltoni et al. 1985 (rat; single dose)	+	+	+	+	+	+	+	+	na	First
Maltoni et al. 1985 (rat; multidose)	+	+	+	+	+	+	+	+	na	First
NTP 1982 (rat)	+	+	++	+	+	++	++	++	na	First
NTP 1982 (mouse)	+	+	++	+	+	++	++	++	na	First
Quast et al. 1983 (mouse)	+	+	++	+	+	++	++	++	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 1,1-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 1,1-dichloroethene and a particular outcome was given an initial confidence rating based on the key features of the individual studies examining that outcome. The presence of these key features of study design was determined for individual studies using four "yes or no" questions in Distiller, which were customized for epidemiology, human controlled exposure, or experimental animal study designs. Separate questionnaires were completed for each outcome assessed in a study. The key features for observational epidemiology (cohort, population, and case-control) studies, human controlled exposure, and experimental animal studies are presented in Tables C-10, C-11, and C-12, respectively. The initial confidence in the study was determined based on the number of key features present in the study design:

- **High Initial Confidence:** Studies in which the responses to the four questions were "yes".

- **Moderate Initial Confidence:** Studies in which the responses to only three of the questions were "yes".

- **Low Initial Confidence:** Studies in which the responses to only two of the questions were "yes".

- **Very Low Initial Confidence:** Studies in which the response to one or none of the questions was "yes".

Table C-10. Key Features of Study Design for Observational Epidemiology Studies

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

Table C-11. Key Features of Study Design for Human-Controlled Exposure Studies

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

Table C-12. Key Features of Study Design for Experimental Animal Studies

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

The presence or absence of the key features and the initial confidence levels for studies examining respiratory, hepatic, and renal effects observed in the observational epidemiology and animal experimental studies are presented in Tables C-13 and C-14, respectively.

A summary of the initial confidence ratings for each outcome is presented in Table C-15. If individual studies for a particular outcome and study type had different study quality ratings, then the highest confidence rating for the group of studies was used to determine the initial confidence rating for the body of evidence; any exceptions were noted in Table C-15.

Table C-13. Presence of Key Features of Study Design for 1,1-Dichloroethene—Observational Epidemiology Studies

Reference	Key features: Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	Initial study confidence
Outcome: Hepatic effects					
Inhalation–cohort					
Ott et al. 1976	No	Yes	Yes	Yes	Moderate
Outcome: Renal effects					
Oral–cross-sectional					
Ott et al. 1976	No	Yes	Yes	Yes	Moderate

Table C-14. Presence of Key Features of Study Design for 1,1-Dichloroethene—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Outcome: Respiratory effects					
Inhalation acute exposure					
Henck et al. 1979 (mouse; Ha[ICR])	Yes	Yes	Yes	Yes	High
Henck et al. 1979 (mouse; B6C3F1)	Yes	Yes	Yes	Yes	High
Henck et al. 1979 (mouse; CD-1)	Yes	Yes	Yes	Yes	High
Henck et al. 1979 (mouse; CF-W)	Yes	Yes	Yes	Yes	High
Zeller et al. 1979a (rat)	No	Yes	No	No	Very Low
Oral acute exposure					
Chieco et al. 1981 (rat)	Yes	No	No	No	Very Low
Forkert and Reynolds 1982 (mouse)	Yes	No	Yes	No	Low
Forkert et al. 1985 (mouse)	Yes	No	Yes	No	Low
Inhalation intermediate exposure					
Gage 1970 (rat)	Yes	No	No	No	Very Low
Maltoni et al. 1985 (rat)	Yes	Yes	No	No	Low

Table C-14. Presence of Key Features of Study Design for 1,1-Dichloroethene—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Key feature: Sufficient number of animals per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
NTP 2015a (rat; 14 weeks)	Yes	Yes	Yes	Yes	High
NTP 2015a (mouse; 17 days)	Yes	Yes	Yes	Yes	High
NTP 2015a (mouse 14 weeks)	Yes	Yes	Yes	Yes	High
Prendergast et al. 1967 (rat)	Yes	Yes	No	No	Low
Prendergast et al. 1967 (guinea pig)	Yes	Yes	No	No	Low
Prendergast et al. 1967 (dog)	Yes	No	No	No	Very Low
Quast et al. 1986 (rat)	Yes	No	No	No	Very Low
Inhalation chronic exposure					
Maltoni et al. 1985 (rat; 104 weeks)	Yes	Yes	No	No	Low
Maltoni et al. 1985 (rat; 52 weeks)	Yes	Yes	No	No	Low
Maltoni et al. 1985 (mouse; 10, 25 ppm)	Yes	Yes	No	No	Low
Maltoni et al. 1985 (mouse; 25 ppm)	Yes	Yes	No	No	Low
Maltoni et al. 1985 (hamster)	Yes	Yes	No	No	Low
NTP 2015a (rat)	Yes	Yes	Yes	Yes	High
NTP 2015a (mouse)	Yes	Yes	Yes	Yes	High
Quast et al. 1986 (rat)	Yes	Yes	No	No	Low
Oral chronic exposure					
Maltoni et al. 1985 (rat; 0.5 mg/kg/day)	Yes	Yes	Yes	No	Moderate
Maltoni et al. 1985 (rat; 5, 10, 20 mg/kg/day)	Yes	Yes	Yes	No	Moderate
NTP 1982 (rat)	Yes	Yes	Yes	Yes	High
NTP 1982 (mouse)	Yes	Yes	Yes	Yes	High
Outcome: Hepatic effects					
Inhalation acute exposure					
Henck et al. 1979 (mouse; Ha[ICR])	Yes	Yes	Yes	Yes	High
Henck et al. 1979 (mouse; B6C3F1)	Yes	Yes	Yes	Yes	High
Henck et al. 1979 (mouse; CD-1)	Yes	Yes	Yes	Yes	High
Henck et al. 1979 (mouse; CF-W)	Yes	Yes	Yes	Yes	High
Jaeger 1977 (rat)	Yes	Yes	No	No	Low
Jaeger et al. 1973a (rat)	Yes	No	No	No	Very Low
Jaeger et al. 1974 (rat; fasted)	No	No	No	No	Very Low
Jaeger et al. 1974 (rat; nonfasted)	No	No	No	No	Very Low

Table C-14. Presence of Key Features of Study Design for 1,1-Dichloroethene—Experimental Animal Studies

Reference	Key feature				Initial study confidence
	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
Maltoni et al. 1985 (mouse)	Yes	Yes	Yes	No	Moderate
McKenna et al. 1978a (rat)	No	No	Yes	No	Very Low
Murray et al. 1979 (rat; 80 ppm)	Yes	Yes	No	Yes	Moderate
Murray et al. 1979 (rat; 160 ppm)	Yes	Yes	No	Yes	Moderate
Murray et al. 1979 (rabbit; 80 ppm)	Yes	Yes	No	Yes	Moderate
Murray et al. 1979 (rabbit; 160 ppm)	Yes	Yes	No	Yes	Moderate
Reitz et al. 1980 (mouse)	No	No	Yes	No	Very Low
Short et al. 1977a, 1977b (rat)	Yes	No	Yes	Yes	Moderate
Short et al. 1977a, 1977b (mouse)	Yes	No	Yes	Yes	Moderate
Oral acute exposure					
Chieco et al. 1981 (rat; 200 mg/kg/day)	Yes	No	Yes	No	Low
Chieco et al. 1981 (rat; 50–200 mg/kg/day)	Yes	No	Yes	No	Low
Jaeger et al. 1973b (rat)	Yes	Yes	No	Yes	Moderate
Jenkins and Andersen 1978 (rat)	Yes	No	No	Yes	Low
Kanz and Reynolds 1986 (rat)	Yes	No	Yes	Yes	Moderate
Kanz et al. 1991 (rat)	Yes	Yes	No	Yes	Moderate
Moslen et al. 1985 (rat)	Yes	No	No	Yes	Low
Murray et al. 1979 (rat)	Yes	Yes	No	Yes	Moderate
NTP 1982 (rat)	Yes	Yes	Yes	No	Moderate
NTP 1982 (mouse)	Yes	Yes	Yes	No	Moderate
Reynolds et al. 1984 (rat)	Yes	No	No	No	Very Low
Inhalation intermediate exposure					
Balmer et al. 1976 (rat)	Yes	Yes	Yes	Yes	High
Gage 1970 (rat)	Yes	No	Yes	No	Low
Maltoni et al. 1985 (rat)	Yes	Yes	No	No	Low
NTP 2015a (rat; 16 days)	Yes	Yes	Yes	Yes	High
NTP 2015a (rat; 14 weeks)	Yes	Yes	Yes	Yes	High
NTP 2015a (mouse; 17 days)	Yes	Yes	Yes	Yes	High
NTP 2015a (mouse; 14 weeks)	Yes	Yes	Yes	Yes	High
Plummer et al. 1990 (rat; continuous)	Yes	No	Yes	No	Low
Plummer et al. 1990 (rat; intermittent)	Yes	No	Yes	No	Low
Prendergast et al. 1967 (monkey)	Yes	Yes	No	No	Low

Table C-14. Presence of Key Features of Study Design for 1,1-Dichloroethene—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Key feature: Sufficient number of animals per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
Prendergast et al. 1967 (rat)	Yes	Yes	No	No	Low
Prendergast et al. 1967 (guinea pig)	Yes	Yes	No	No	Low
Prendergast et al. 1967 (dog)	Yes	No	No	No	Very Low
Quast 1976 (rat)	Yes	Yes	Yes	Yes	High
Quast et al. 1986 (rat)	Yes	No	Yes	Yes	Moderate
Oral intermediate exposure					
NTP 1982 (rat)	Yes	Yes	Yes	Yes	High
NTP 1982 (mouse)	Yes	Yes	Yes	Yes	High
Quast et al. 1983 (dog)	Yes	Yes	Yes	Yes	High
Inhalation chronic exposure					
Lee et al. 1977, 1978 (rat)	Yes	Yes	Yes	No	Moderate
Lee et al. 1977, 1978 (mouse)	Yes	Yes	Yes	No	Moderate
Maltoni et al. 1985 (rat; 104 weeks)	Yes	Yes	No	No	Low
Maltoni et al. 1985 (rat; 52 weeks)	Yes	Yes	No	No	Low
Maltoni et al. 1985 (mouse; 10, 25 ppm)	Yes	Yes	No	No	Low
Maltoni et al. 1985 (mouse; 25 ppm)	Yes	Yes	No	No	Low
Maltoni et al. 1985 (hamster)	Yes	Yes	No	No	Low
NTP 2015a (rat; 105 weeks)	Yes	Yes	Yes	Yes	High
NTP 2015a (mouse; 105 weeks)	Yes	Yes	Yes	Yes	High
Quast et al. 1986 (rat)	Yes	Yes	Yes	Yes	High
Oral chronic exposure					
Maltoni et al. 1985 (rat; 0.5 mg/kg/day)	Yes	Yes	Yes	No	Moderate
Maltoni et al. 1985 (rat; multidose)	Yes	Yes	Yes	No	Moderate
NTP 1982 (rat)	Yes	Yes	Yes	Yes	High
NTP 1982 (mouse)	Yes	Yes	Yes	Yes	High
Quast et al. 1983 (rat)	Yes	Yes	Yes	Yes	High
Outcome: Renal effects					
Inhalation acute exposure					
Henck et al. 1979 (mouse; Ha[ICR])	Yes	Yes	Yes	Yes	High
Henck et al. 1979 (mouse; B6C3F1)	Yes	Yes	Yes	Yes	High
Henck et al. 1979 (mouse; CD-1)	Yes	Yes	Yes	Yes	High
Henck et al. 1979 (mouse; CF-W)	Yes	Yes	Yes	Yes	High

Table C-14. Presence of Key Features of Study Design for 1,1-Dichloroethene—Experimental Animal Studies

Reference	Key feature				Initial study confidence
	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
Jackson and Conolly 1985 (rat)	Yes	Yes	Yes	Yes	High
Maltoni et al. 1985 (mouse)	Yes	Yes	Yes	No	Moderate
McKenna et al. 1978a (rat)	No	No	Yes	No	Very Low
Short et al. 1977a, 1977b (rat)	Yes	No	Yes	Yes	Moderate
Short et al. 1977a, 1977b (mouse)	Yes	No	Yes	Yes	Moderate
Oral acute exposure					
Chieco et al. 1981 (rat)	Yes	No	Yes	No	Low
Jenkins and Andersen 1978 (rat; single dose)	Yes	No	Yes	Yes	Moderate
Jenkins and Andersen 1978 (rat; multidose)	Yes	No	Yes	Yes	Moderate
Jenkins and Andersen 1978 (rat; single dose)	Yes	No	Yes	Yes	Moderate
Inhalation intermediate exposure					
Maltoni et al. 1985 (rat)	Yes	Yes	No	No	Low
NTP 2015a (rat; 16 days)	Yes	Yes	Yes	Yes	High
NTP 2015a (rat; 14 weeks)	Yes	Yes	Yes	Yes	High
NTP 2015a (mouse; 17 days)	Yes	Yes	Yes	Yes	High
NTP 2015a (mouse; 14 weeks)	Yes	Yes	Yes	Yes	High
Prendergast et al. 1967 (rat)	Yes	Yes	No	No	Low
Prendergast et al. 1967 (dog)	Yes	No	No	No	Very Low
Oral intermediate exposure					
Quast et al. 1983 (dog)	Yes	Yes	Yes	Yes	High
Inhalation chronic exposure					
Maltoni et al. 1985 (rat; 104 weeks)	Yes	Yes	No	No	Low
Maltoni et al. 1985 (rat; 52 weeks)	Yes	Yes	No	No	Low
Maltoni et al. 1985 (mouse; 10, 25 ppm)	Yes	Yes	No	No	Low
Maltoni et al. 1985 (mouse; 25 ppm)	Yes	Yes	No	No	Low
Maltoni et al. 1985 (hamster)	Yes	Yes	No	No	Low
NTP 2015a (rat; 105 weeks)	Yes	Yes	Yes	Yes	High
NTP 2015a (mouse; 105 weeks)	Yes	Yes	Yes	Yes	High
Quast et al. 1986 (rat)	Yes	Yes	Yes	Yes	High

Table C-14. Presence of Key Features of Study Design for 1,1-Dichloroethene—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Key feature: Sufficient number of animals per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
Oral chronic exposure					
Maltoni et al. 1985 (rat; single dose)	Yes	Yes	Yes	No	Moderate
Maltoni et al. 1985 (rat; multidose)	Yes	Yes	Yes	No	Moderate
NTP 1982 (rat)	Yes	Yes	Yes	Yes	High
NTP 1982 (mouse)	Yes	Yes	Yes	Yes	High
Quast et al. 1983 (mouse)	Yes	Yes	Yes	Yes	High

Table C-15. Initial Confidence Rating for 1,1-Dichloroethene Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Respiratory effects		
Inhalation acute exposure		
Animal studies		
Henck et al. 1979 (mouse; Ha[ICR])	High	High
Henck et al. 1979 (mouse; B6C3F1)	High	
Henck et al. 1979 (mouse; CD-1)	High	
Henck et al. 1979 (mouse; CF-W)	High	
Zeller et al. 1979a (rat)	Very Low	
Inhalation intermediate exposure		
Animal studies		
Gage 1970 (rat)	Very Low	High
Maltoni et al. 1985 (rat)	Low	
NTP 2015a (rat; 14 weeks)	High	
NTP 2015a (mouse; 17 days)	High	
NTP 2015a (mouse 14 weeks)	High	
Prendergast et al. 1967 (rat)	Low	
Prendergast et al. 1967 (guinea pig)	Low	
Prendergast et al. 1967 (dog)	Very Low	
Quast et al. 1986 (rat)	Very Low	

Table C-15. Initial Confidence Rating for 1,1-Dichloroethene Health Effects Studies

	Initial study confidence	Initial confidence rating
Inhalation chronic exposure		
Animal studies		
Maltoni et al. 1985 (rat; 104 weeks)	Low	High
Maltoni et al. 1985 (rat; 52 weeks)	Low	
Maltoni et al. 1985 (mouse; 10, 25 ppm)	Low	
Maltoni et al. 1985 (mouse; 25 ppm)	Low	
Maltoni et al. 1985 (hamster)	Low	
NTP 2015a (rat)	High	
NTP 2015a (mouse)	High	
Quast et al. 1986 (rat)	Low	
Oral acute exposure		
Animal studies		
Chieco et al. 1981 (rat)	Very Low	Low
Forkert and Reynolds 1982 (mouse)	Low	
Forkert et al. 1985 (mouse)	Low	
Oral chronic exposure		
Animal studies		
Maltoni et al. 1985 (rat; 0.5 mg/kg/day)	Moderate	High
Maltoni et al. 1985 (rat; 5, 10, 20 mg/kg/day)	Moderate	
NTP 1982 (rat)	High	
NTP 1982 (mouse)	High	
Outcome: Hepatic effects		
Inhalation acute exposure		
Animal studies		
Henck et al. 1979 (mouse; Ha[ICR])	High	High
Henck et al. 1979 (mouse; B6C3F1)	High	
Henck et al. 1979 (mouse; CD-1)	High	
Henck et al. 1979 (mouse; CF-W)	High	
Jaeger 1977 (rat)	Low	
Jaeger et al. 1973a (rat)	Very Low	
Jaeger et al. 1974 (rat; fasted)	Very Low	
Jaeger et al. 1974 (rat; nonfasted)	Very Low	
Maltoni et al. 1985 (mouse)	Moderate	
McKenna et al. 1978a (rat)	Very Low	
Murray et al. 1979 (rat; 80 ppm)	Moderate	
Murray et al. 1979 (rat; 160 ppm)	Moderate	
Murray et al. 1979 (rabbit; 80 ppm)	Moderate	
Murray et al. 1979 (rabbit; 160 ppm)	Moderate	
Reitz et al. 1980 (mouse)	Very Low	

Table C-15. Initial Confidence Rating for 1,1-Dichloroethene Health Effects Studies

	Initial study confidence	Initial confidence rating
Short et al. 1977a, 1977b (rat)	Moderate	
Short et al. 1977a, 1977b (mouse)	Moderate	
Inhalation intermediate exposure		
Animal studies		
Balmer et al. 1976 (rat)	High	High
Gage 1970 (rat)	Low	
Maltoni et al. 1985 (rat)	Low	
NTP 2015a (rat; 16 days)	High	
NTP 2015a (rat; 14 weeks)	High	
NTP 2015a (mouse; 17 days)	High	
NTP 2015a (mouse; 14 weeks)	High	
Plummer et al. 1990 (rat; continuous)	Low	
Plummer et al. 1990 (rat; intermittent)	Low	
Prendergast et al. 1967 (monkey)	Low	
Prendergast et al. 1967 (rat)	Low	
Prendergast et al. 1967 (guinea pig)	Low	
Prendergast et al. 1967 (dog)	Very Low	
Quast 1976 (rat)	High	
Quast 1986 (rat)	Moderate	
Inhalation chronic exposure		
Human studies		
Ott et al. 1976	Moderate	Moderate
Animal studies		
Lee et al. 1977, 1978 (rat)	Moderate	High
Lee et al. 1977, 1978 (mouse)	Moderate	
Maltoni et al. 1985 (rat; 104 weeks)	Low	
Maltoni et al. 1985 (rat; 52 weeks)	Low	
Maltoni et al. 1985 (mouse; 10, 25 ppm)	Low	
Maltoni et al. 1985 (mouse; 25 ppm)	Low	
Maltoni et al. 1985 (hamster)	Low	
NTP 2015a (rat; 105 weeks)	High	
NTP 2015a (mouse; 105 weeks)	High	
Quast et al. 1986 (rat)	High	
Oral acute exposure		
Animal studies		
Chieco et al. 1981 (rat; 200 mg/kg/day)	Low	Moderate
Chieco et al. 1981 (rat; 50–200 mg/kg/day)	Low	
Jaeger et al. 1973b (rat)	Moderate	
Jenkins and Andersen 1978 (rat)	Low	

Table C-15. Initial Confidence Rating for 1,1-Dichloroethene Health Effects Studies

	Initial study confidence	Initial confidence rating
Kanz and Reynolds 1986 (rat)	Moderate	
Kanz et al. 1991 (rat)	Moderate	
Moslen et al. 1985 (rat)	Low	
Murray et al. 1979 (rat)	Moderate	
NTP 1982 (rat)	Moderate	
NTP 1982 (mouse)	Moderate	
Reynolds et al. 1984 (rat)	Very Low	
Oral intermediate exposure		
Animal studies		
NTP 1982 (rat)	High	
NTP 1982 (mouse)	High	High
Quast et al. 1983 (dog)	High	
Oral chronic exposure		
Animal studies		
Maltoni et al. 1985 (rat; 0.5 mg/kg/day)	Moderate	
Maltoni et al. 1985 (rat; multidose)	Moderate	
NTP 1982 (rat)	High	High
NTP 1982 (mouse)	High	
Quast et al. 1983 (rat)	High	
Outcome: Renal effects		
Inhalation acute exposure		
Animal studies		
Henck et al. 1979 (mouse; Ha[ICR])	High	
Henck et al. 1979 (mouse; B6C3F1)	High	
Henck et al. 1979 (mouse; CD-1)	High	
Henck et al. 1979 (mouse; CF-W)	High	
Jackson and Conolly 1985 (rat)	High	High
Maltoni et al. 1985 (mouse)	Moderate	
McKenna et al. 1978a (rat)	Very Low	
Short et al. 1977a, 1977b (rat)	Moderate	
Short et al. 1977a, 1977b (mouse)	Moderate	
Inhalation intermediate exposure		
Animal studies		
Maltoni et al. 1985 (rat)	Low	
NTP 2015a (rat; 16 days)	High	
NTP 2015a (rat; 14 weeks)	High	High
NTP 2015a (mouse; 17 days)	High	
NTP 2015a (mouse; 14 weeks)	High	
Prendergast et al. 1967 (rat)	Low	

Table C-15. Initial Confidence Rating for 1,1-Dichloroethene Health Effects Studies

	Initial study confidence	Initial confidence rating
Prendergast et al. 1967 (dog)	Very Low	
Inhalation chronic exposure		
Human studies		
Ott et al. 1976	Moderate	Moderate
Animal studies		
Maltoni et al. 1985 (rat; 104 weeks)	Low	High
Maltoni et al. 1985 (rat; 52 weeks)	Low	
Maltoni et al. 1985 (mouse; 10, 25 ppm)	Low	
Maltoni et al. 1985 (mouse; 25 ppm)	Low	
Maltoni et al. 1985 (hamster)	Low	
NTP 2015a (rat; 105 weeks)	High	
NTP 2015a (mouse; 105 weeks)	High	
Quast et al. 1986 (rat)	High	
Oral acute exposure		
Animal studies		
Chieco et al. 1981 (rat)	Low	Moderate
Jenkins and Andersen 1978 (rat; single dose)	Moderate	
Jenkins and Andersen 1978 (rat; multidose)	Moderate	
Jenkins and Andersen 1978 (rat; single dose)	Moderate	
Oral intermediate exposure		
Animal studies		
Quast et al. 1983 (dog)	High	High
Oral chronic exposure		
Animal studies		
Maltoni et al. 1985 (rat; single dose)	Moderate	High
Maltoni et al. 1985 (rat; multidose)	Moderate	
NTP 1982 (rat)	High	
NTP 1982 (mouse)	High	
Quast et al. 1983 (mouse)	High	

C.6.2 Adjustment of the Confidence Rating

The initial confidence rating was then downgraded or upgraded depending on whether there were substantial issues that would decrease or increase confidence in the body of evidence. The nine properties of the body of evidence that were considered are listed below. The summaries of the assessment of the confidence in the body of evidence for respiratory, hepatic, renal, and cancer effects are presented in Table C-16. If the confidence ratings for a particular outcome were based on more than one type of human study, then the highest confidence rating was used for subsequent analyses. An overview of the confidence in the body of evidence for all health effects associated with 1,1-dichloroethene exposure is presented in Table C-17.

Table C-16. Adjustments to the Initial Confidence in the Body of Evidence

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Outcome: Respiratory effects			
Animal studies	High	None	High
Outcome: Hepatic effects			
Human studies	Moderate	None	Moderate
Animal studies	High	+1 consistency in findings	High
Outcome: Renal effects			
Human studies	Moderate	None	Moderate
Animal studies	High	+1 consistency in findings	High

Table C-17. Confidence in the Body of Evidence for 1,1-Dichloroethene

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

Five properties of the body of evidence were considered to determine whether the confidence rating should be downgraded:

- **Risk of bias.** Evaluation of whether there is substantial risk of bias across most of the studies examining the outcome. This evaluation used the risk of bias tier groupings for individual studies examining a particular outcome (Tables C-8 and C-9). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for risk of bias:
    - No downgrade if most studies are in the risk of bias first tier
    - Downgrade one confidence level if most studies are in the risk of bias second tier
    - Downgrade two confidence levels if most studies are in the risk of bias third tier

- **Unexplained inconsistency.** Evaluation of whether there is inconsistency or large variability in the magnitude or direction of estimates of effect across studies that cannot be explained. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for unexplained inconsistency:
    - No downgrade if there is little inconsistency across studies or if only one study evaluated the outcome
    - Downgrade one confidence level if there is variability across studies in the magnitude or direction of the effect
    - Downgrade two confidence levels if there is substantial variability across studies in the magnitude or direct of the effect

- **Indirectness.** Evaluation of four factors that can affect the applicability, generalizability, and relevance of the studies:
    - Relevance of the animal model to human health—unless otherwise indicated, studies in rats, mice, and other mammalian species are considered relevant to humans
    - Directness of the endpoints to the primary health outcome—examples of secondary outcomes or nonspecific outcomes include organ weight in the absence of histopathology or clinical chemistry findings in the absence of target tissue effects
    - Nature of the exposure in human studies and route of administration in animal studies—inhalation, oral, and dermal exposure routes are considered relevant unless there are compelling data to the contrary
    - Duration of treatment in animal studies and length of time between exposure and outcome assessment in animal and prospective human studies—this should be considered on an outcome-specific basis

  Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for indirectness:
    - No downgrade if none of the factors are considered indirect
    - Downgrade one confidence level if one of the factors is considered indirect
    - Downgrade two confidence levels if two or more of the factors are considered indirect

- **Imprecision.** Evaluation of the narrowness of the effect size estimates and whether the studies have adequate statistical power. Data are considered imprecise when the ratio of the upper to lower 95% CIs for most studies is ≥10 for tests of ratio measures (e.g., odds ratios) and ≥100 for absolute measures (e.g., percent control response). Adequate statistical power is determined if the study can detect a potentially biologically meaningful difference between groups (20% change from control response for categorical data or risk ratio of 1.5 for continuous data). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for imprecision:
    - No downgrade if there are no serious imprecisions
    - Downgrade one confidence level for serious imprecisions
    - Downgrade two confidence levels for very serious imprecisions

- **Publication bias.** Evaluation of the concern that studies with statistically significant results are more likely to be published than studies without statistically significant results.
    - Downgrade one level of confidence for cases where there is serious concern with publication bias

Four properties of the body of evidence were considered to determine whether the confidence rating should be upgraded:

- **Large magnitude of effect.** Evaluation of whether the magnitude of effect is sufficiently large so that it is unlikely to have occurred as a result of bias from potential confounding factors.
    - Upgrade one confidence level if there is evidence of a large magnitude of effect in a few studies, provided that the studies have an overall low risk of bias and there is no serious unexplained inconsistency among the studies of similar dose or exposure levels; confidence can also be upgraded if there is one study examining the outcome, provided that the study has an overall low risk of bias

- **Dose response.** Evaluation of the dose-response relationships measured within a study and across studies. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
    - Upgrade one confidence level for evidence of a monotonic dose-response gradient
    - Upgrade one confidence level for evidence of a non-monotonic dose-response gradient where there is prior knowledge that supports a non-monotonic dose-response and a non-monotonic dose-response gradient is observed across studies

- **Plausible confounding or other residual biases.** This factor primarily applies to human studies and is an evaluation of unmeasured determinants of an outcome such as residual bias towards the null (e.g., "healthy worker" effect) or residual bias suggesting a spurious effect (e.g., recall bias). Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
    - Upgrade one confidence level for evidence that residual confounding or bias would underestimate an apparent association or treatment effect (i.e., bias toward the null) or suggest a spurious effect when results suggest no effect

- **Consistency in the body of evidence.** Evaluation of consistency across animal models and species, consistency across independent studies of different human populations and exposure scenarios, and consistency across human study types. Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:

Upgrade one confidence level if there is a high degree of consistency in the database

C.7 TRANSLATE CONFIDENCE RATING INTO LEVEL OF EVIDENCE OF HEALTH EFFECTS

In the seventh step of the systematic review of the health effects data for 1,1-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 1,1-dichloroethene is presented in Table C-18.

Table C-18. Level of Evidence of Health Effects for 1,1-Dichloroethene

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human studies			
Hepatic effects	Moderate	No effect	Inadequate
Renal effects	Moderate	No effect	Inadequate
Animal studies			
Respiratory effects	High	Health effect	High
Hepatic effects	High	Health effect	High
Renal effects	High	Health effect	High

C.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

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

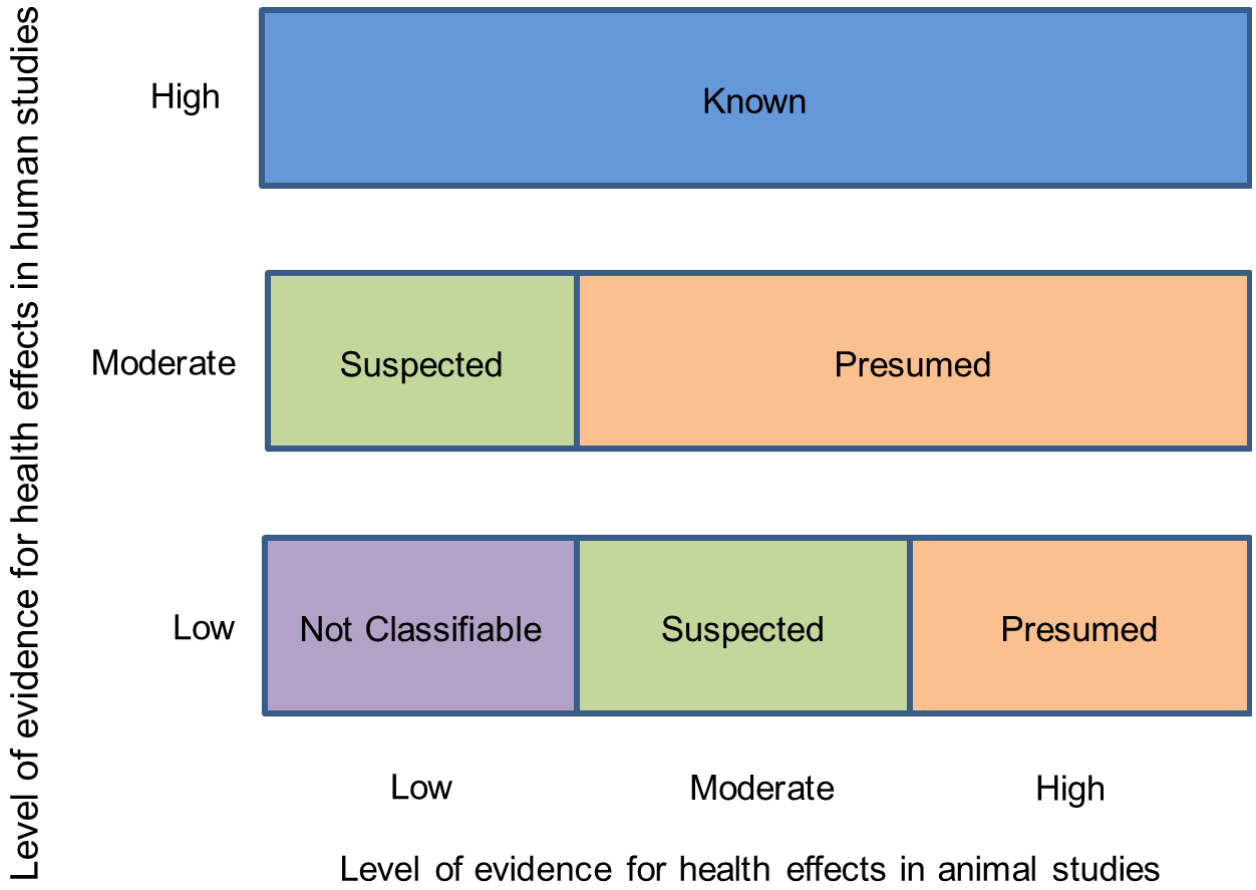
- **Known** to be a hazard to humans
- **Presumed** to be a hazard to humans
- **Suspected** to be a hazard to humans
- **Not classifiable** as to the hazard to humans

The initial hazard identification was based on the highest level of evidence in the human studies and the level of evidence in the animal studies; if there were no data for one evidence stream (human or animal), then the hazard identification was based on the one data stream (equivalent to treating the missing evidence stream as having low level of evidence). The hazard identification scheme is presented in Figure C-1 and described below:

- **Known:** A health effect in this category would have:
  - High level of evidence for health effects in human studies **AND** a high, moderate, or low level of evidence in animal studies.
- **Presumed:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** high or moderate level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** high level of evidence in animal studies
- **Suspected:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** low level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** moderate level of evidence in animal studies
- **Not classifiable:** A health effect in this category would have:
  - Low level of evidence in human studies **AND** low level of evidence in animal studies

Other relevant data such as mechanistic or mode-of-action data were considered to raise or lower the level of the hazard identification conclusion by providing information that supported or opposed biological plausibility.

Figure C-1. Hazard Identification Scheme



Two hazard identification conclusion categories were used when the data indicated that there may be no health effect in humans:

- **Not identified** to be a hazard in humans
- **Inadequate** to determine hazard to humans

If the human level of evidence conclusion of no health effect was supported by the animal evidence of no health effect, then the hazard identification conclusion category of "not identified" was used. If the human or animal level of evidence was considered inadequate, then a hazard identification conclusion category of "inadequate" was used. As with the hazard identification for health effects, the impact of other relevant data was also considered for no health effect data.

The hazard identification conclusions for 1,1-dichloroethene are listed below and summarized in Table C-19.

Table C-19. Hazard Identification Conclusions for 1,1-Dichloroethene

Outcome	Hazard identification
Respiratory effects	Presumed health effect
Hepatic effects	Presumed health effect
Renal effects	Presumed health effect

Presumed Health Effects

- Respiratory effects
  - No human data
  - High level of evidence of nasal lesions in rats and mice following intermediate- and chronic-duration inhalation exposure (NTP 2015a)
- Hepatic effects
  - Inadequate human data; one study did not find evidence of hepatotoxicity in a cohort of workers exposed to 1,1-dichloroethene (Ott et al. 1976).
  - High level of evidence from inhalation or oral exposure of laboratory animals (e.g., Henck et al. 1979; NTP 1982, 2015a; Prendergast et al. 1967; Quast et al. 1983; Short et al. 1977a, 1977b).
  - 1,1-Dichloroethene was significantly more toxic to the kidney of rats that were fasted prior to exposure.
- Renal effects
  - Inadequate human data; one study did not find evidence of renal toxicity in a cohort of workers exposed to 1,1-dichloroethene (Ott et al. 1976).
  - High level of evidence from inhalation exposure of laboratory animals (e.g., Henck et al. 1979; Maltoni et al. 1985; NTP 2015a; Prendergast et al. 1967; Short et al. 1977a, 1977b).
  - 1,1-Dichloroethene was significantly more toxic to the kidney of mice than rats.

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 C-5)

(1) Route of exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically, when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure (i.e., inhalation, oral, and dermal). LSE figures are limited to the inhalation and oral routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures. Profiles with more than one chemical may have more LSE tables and figures.

(2) Exposure period. Three exposure periods—acute (<15 days), intermediate (15–364 days), and chronic (≥365 days)—are presented within each relevant route of exposure. In this example, two oral studies of chronic-duration exposure are reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Figure key. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 51 identified NOAELs and less serious LOAELs (also see the three "51R" data points in sample LSE Figure 2-X).

(4) Species (strain) No./group. The test species (and strain), whether animal or human, are identified in this column. The column also contains information on the number of subjects and sex per group. Chapter 1, Relevance to Public Health, covers the relevance of animal data to human toxicity and Section 3.1, Toxicokinetics, contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(5) Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 51), rats were orally exposed to “Chemical X” via feed for 2 years. For a

more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Aida et al. 1992).

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), behavioral (BH), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), enzyme activity (EA), food intake (FI), fetal toxicity (FX), gross necropsy (GN), hematology (HE), histopathology (HP), lethality (LE), maternal toxicity (MX), organ function (OF), ophthalmology (OP), organ weight (OW), teratogenicity (TG), urinalysis (UR), and water intake (WI).

(7) Endpoint. This column lists the endpoint examined. The major categories of health endpoints included in LSE tables and figures are death, body weight, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, developmental, other noncancer, and cancer. "Other noncancer" refers to any effect (e.g., alterations in blood glucose levels) not covered in these systems. In the example of key number 51, three endpoints (body weight, hematological, and hepatic) were investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. The body weight effect reported in key number 51 is a NOAEL at 25.5 mg/kg/day. NOAELs are not reported for cancer and death; with the exception of these two endpoints, this field is left blank if no NOAEL was identified in the study.

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. Key number 51 reports a less serious LOAEL of 6.1 mg/kg/day for the hepatic system, which was used to derive a chronic exposure, oral MRL of 0.008 mg/kg/day (see footnote "c"). MRLs are not derived from serious LOAELs. A cancer effect level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases. If no LOAEL/CEL values were identified in the study, this field is left blank.

(10) Reference. The complete reference citation is provided in Chapter 8 of the profile.

(11) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. For example, footnote "c" indicates that the LOAEL of 6.1 mg/kg/day in key number 51 was used to derive an oral MRL of 0.008 mg/kg/day.

FIGURE LEGEND

See Sample LSE Figure (page C-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)

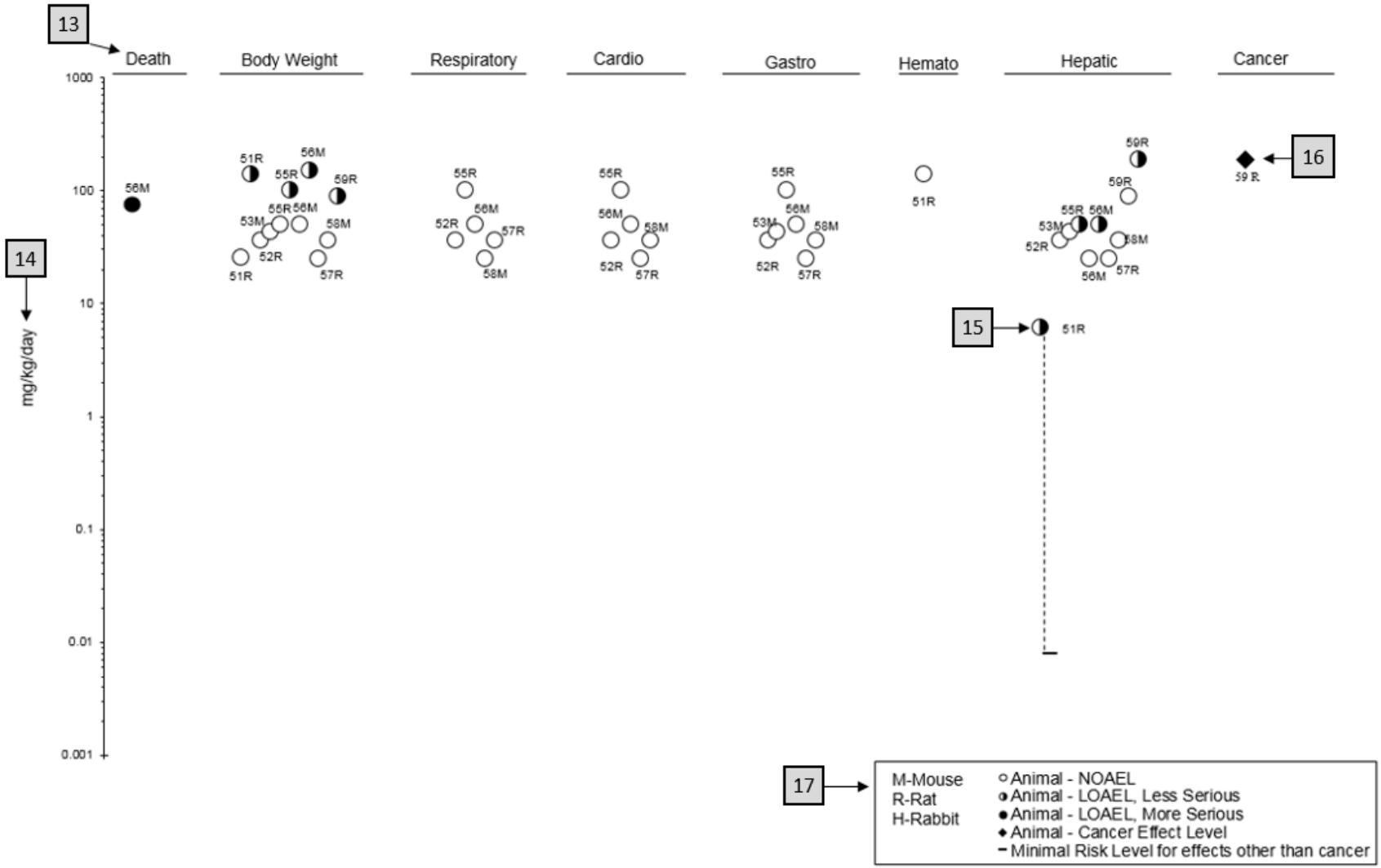
Figure key[a] (3)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 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

The following additional materials are available online:

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) provides support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/.

APPENDIX F. GLOSSARY

Absorption—The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to the taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of ≤14 days, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD) or Benchmark Concentration (BMC)—is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a BMD_{10} would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

Cancer Effect Level (CEL)—The lowest dose of a chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

Case Report—A report that describes a single individual with a particular disease or exposure. These reports may suggest some potential topics for scientific research but are not actual research studies.

Case Series—Reports that describe the experience of a small number of individuals with the same disease or exposure. These reports may suggest potential topics for scientific research but are not actual research studies.

Ceiling Value—A concentration that must not be exceeded.

Chronic Exposure—Exposure to a chemical for ≥365 days, as specified in the Toxicological Profiles.

Clastogen—A substance that causes breaks in chromosomes resulting in addition, deletion, or rearrangement of parts of the chromosome.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at a specific point in time.

Data Needs—Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the response or amount of the response.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

Epidemiology—The investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Excretion—The process by which metabolic waste products are removed from the body.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one-half of a quantity of a chemical from the body or environmental media.

Health Advisory—An estimate of acceptable drinking water levels for a chemical substance derived by EPA and based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

Immunotoxicity—Adverse effect on the functioning of the immune system that may result from exposure to chemical substances.

Incidence—The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

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

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

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

Metabolism—Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—The state of being diseased; the morbidity rate is the incidence or prevalence of a disease in a specific population.

Mortality—Death; the mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations, which are changes in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a hazardous substance.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Although effects may be produced at this dose, they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio that is greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic endpoints. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—A type of physiologically based dose-response model that is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which a group is followed over time and the pertinent observations are made on events occurring after the start of the study.

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation RfC is expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). RQs are (1) ≥1 pound or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

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

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio/Relative Risk—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio that is greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

Toxicokinetic—The absorption, distribution, metabolism, and elimination of toxic compounds in the living organism.

Toxics Release Inventory (TRI)—The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

Xenobiotic—Any substance that is foreign to the biological system.

APPENDIX G. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	American Association of Poison Control Centers
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ACMT	American College of Medical Toxicology
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AIC	Akaike's information criterion
AIHA	American Industrial Hygiene Association
ALT	alanine aminotransferase
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BCF	bioconcentration factor
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
C	centigrade
CAA	Clean Air Act
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
cm	centimeter
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
ERPG	emergency response planning guidelines
F	Fahrenheit
F1	first-filial generation
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FR	Federal Register

FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GGT	γ-glutamyl transferase
GRAS	generally recognized as safe
HEC	human equivalent concentration
HED	human equivalent dose
HHS	Department of Health and Human Services
HPLC	high-performance liquid chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Level of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
MRL	Minimal Risk Level
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
Mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NCEH	National Center for Environmental Health
ND	not detected
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences

NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEHSU	Pediatric Environmental Health Specialty Unit
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure 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