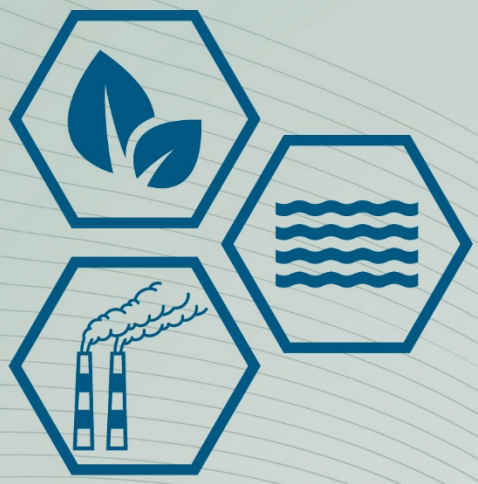

Toxicological Profile for 1,2-Dichloropropane

November 2021

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

CS274127-A

DISCLAIMER

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

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
November 2021	Final toxicological profile released
December 2019	Draft for public comment toxicological profile released
December 1989	Final toxicological profile released

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

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

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

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CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

1,2-Dichloropropane (CAS Registry Number 78-87-5) is a colorless liquid belonging to a class of volatile organic compounds (VOCs). It has a chloroform-like odor and evaporates quickly at room temperature. 1,2-Dichloropropane is used in the United States as a chemical intermediate and in the manufacture of chlorinated and industrial solvents. A few consumer products contain 1,2-dichloropropane, including household stain removers and waxes and sealants for natural stone and other surfaces. Before the early 1980s, 1,2-dichloropropane was used in farming as a soil fumigant. Most of the 1,2-dichloropropane released into the environment ends up in the air or groundwater. The greatest potential for the general population to be exposed to 1,2-dichloropropane is through inhalation of contaminated ambient air and consumption of contaminated drinking water. The general population may also be exposed while using consumer products containing 1,2-dichloropropane. Occupational exposure to 1,2-dichloropropane may result during its production, use in chemical reactions, use as an industrial solvent, and disposal of processing wastes containing the chemical. Workers involved in cleaning up hazardous waste or spill sites that contain 1,2-dichloropropane may potentially be exposed.

1.2 SUMMARY OF HEALTH EFFECTS

Information on the noncancer toxicity of 1,2-dichloropropane comes primarily from studies in laboratory animals; however, several case reports in exposed humans contribute to the identification of primary toxicity targets. Eighty-six laboratory animal toxicity studies with health effects data have been identified: 51 inhalation, 32 oral, and 5 dermal.

As illustrated in Figures 1-1 and 1-2, sensitive targets in laboratory animals following inhalation or oral exposure include the upper respiratory tract (nasal) damage, liver damage, anemia, central nervous system (CNS) depression, and delayed ossification in fetuses. In general, the kidney does not appear to be a sensitive target in laboratory animals, but renal failure has been associated with high oral doses of 1,2-dichloropropane in human case reports. A systematic review of these endpoints resulted in the following hazard identification conclusions:

- Upper respiratory tract effects are a presumed health effect for humans following inhalation exposure.
- Hematological effects are a presumed health effect for humans.

- Hepatic effects are a presumed health effect for humans.
- CNS depression is a presumed health effect for humans.
- Developmental effects are a presumed health effect for humans.
- The data are inadequate to conclude whether renal effects will occur in humans.

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

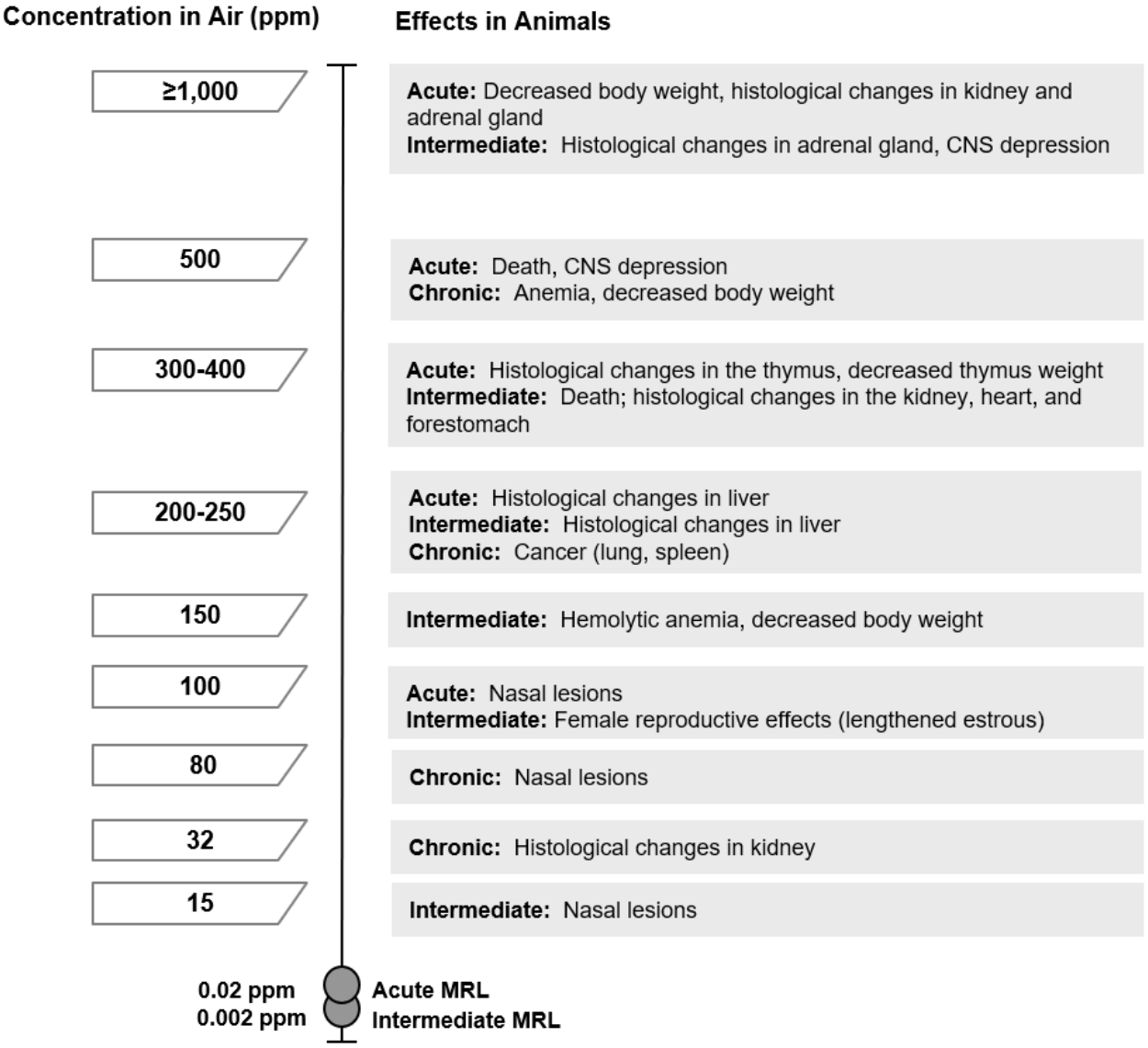
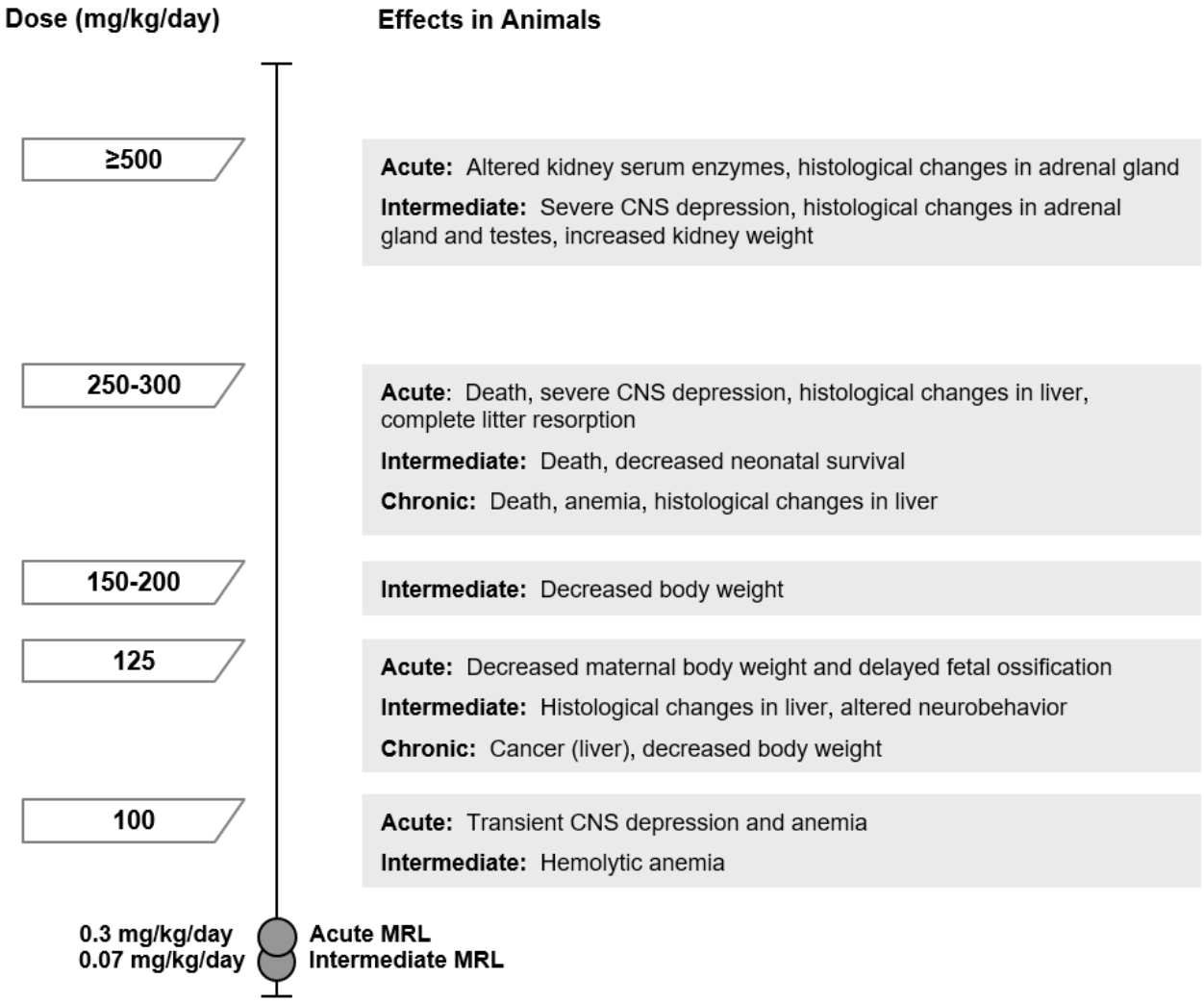


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to 1,2-Dichloropropane



Respiratory Effects. Limited data from chemical spill accident reports indicate that exposure to high concentrations of 1,2-dichloropropane can cause respiratory tract irritation in humans (ACGIH 2014; Rubin 1988). In laboratory animals, the upper respiratory tract is a sensitive target tissue following acute-, intermediate- and chronic-duration inhalation exposure (Matsumoto et al. 2013; Nitschke and Johnson 1983; Nitschke et al. 1988; Umeda et al. 2010). Rats are the most sensitive species, with degeneration of the olfactory mucosa observed at the lowest acute-duration concentration tested (100 ppm), hyperplasia of the nasal respiratory epithelium observed at the lowest intermediate-duration concentration tested (15 ppm), and atrophy of olfactory epithelium, inflammation of the respiratory epithelium, squamous cell metaplasia of respiratory epithelium, and hyperplasia of the transitional epithelium at the lowest chronic-duration concentration tested (80 ppm); additional effects observed at higher concentrations included squamous cell hyperplasia, degeneration of the olfactory epithelium, and inflammation and hyperplasia of the submucosal glands (Nitschke et al. 1988; Umeda et al. 2010). Similar nasal lesions were also observed in mice and rabbits following acute- or intermediate-duration exposure to concentrations ≥300 and 1,000 ppm, respectively (Nitschke and Johnson 1983; Nitschke et al. 1988), and in mice following chronic-duration exposure to concentrations ≥80 ppm (Matsumoto et al. 2013). The upper respiratory tract has not been assessed in animals following oral exposure to 1,2-dichloropropane.

Hematological Effects. Hemolytic anemia as well as incidences of disseminated intravascular coagulation have been reported in humans following accidental or intentional acute exposure to high levels of 1,2-dichloropropane via ingestion (Di Nucci et al. 1988; Perbellini et al. 1985), inhalation (Lucantoni et al. 1991, 1992; Pozzi et al. 1985), or dermal exposure (Fiaccadori et al. 2003), some of which were fatal. Exposure levels in these cases are unknown but are assumed to be high. Data from animal studies show that exposure to 1,2-dichloropropane at inhalation concentrations as low as 150 ppm or oral doses as low as 100 mg/kg/day result in hemolytic anemia in rats, mice, and rabbits (Berdasco et al. 1988; Bruckner et al. 1989; Imberti et al. 1990; Kirk et al. 1990, 1995; Matsumoto et al. 2013; Nitschke et al. 1988; Umeda et al. 2010).

Hepatic Effects. One of the principal target organs for the toxicity of 1,2-dichloropropane in both humans and animals is the liver. Numerous cases studies reported hepatic effects following occupational exposure, accidental or intentional ingestion, intentional inhalation abuse (“sniffing” or “huffing”), or prolonged dermal exposure to large amounts of mixtures containing 1,2-dichloropropane (Chiappino and Secchi 1968; Di Nucci et al. 1988; Fiaccadori et al. 2003; Larcan et al. 1977; Lucantoni et al. 1991, 1992; Kubo et al. 2015; Perbellini et al. 1985; Pozzi et al. 1985; Secchi and Alessio 1968; Thorel et al. 1986).

Observed effects in humans include altered serum liver enzymes, impaired liver function, toxic hepatitis, hepatic necrosis, and liver failure. In laboratory animals, hepatic lesions were consistently observed following exposure to 1,2-dichloropropane at inhalation concentrations of ≥250 ppm and oral doses ≥12 mg/kg/day (see Section 2.9 for references). Observed effects in animals were primarily fatty degeneration and necrosis.

Renal Effects. A few case reports of intentional or accidental 1,2-dichloropropane poisoning suggest that the kidney is a target organ of toxicity in humans (Di Nucci et al. 1988; Perbellini et al. 1985; Pozzi et al. 1985). Observed effects included impaired kidney function, tubular necrosis, and acute kidney failure. Exposure levels in these cases are unknown but are assumed to be high. However, the kidney does not appear to be a sensitive target of 1,2-dichloropropane in laboratory animals. Inconsistent findings of kidney damage were observed following inhalation exposure to 1,2-dichloropropane in laboratory animals, with most studies observing renal effects (fatty degeneration) only at concentrations ≥1,000 ppm (Heppel et al. 1946a, 1948; Highman and Heppel 1946); however, a chronic study in mice reported basophilic changes and cortical mineralization in males at concentrations ≥32 ppm (Matsumoto et al. 2013). No adverse renal effects were observed in laboratory animals in any available oral studies (Bruckner et al. 1989; Gi et al. 2015a; Gorzinski and Johnson 1989; Kirk et al. 1990; NTP 1986).

Neurological Effects. The CNS is a target for 1,2-dichloropropane toxicity in both humans and animals. Severe CNS depression and coma are associated with accidental or intentional ingestion or inhalation of large quantities of 1,2-dichloropropane (Larcan et al. 1977; Perbellini et al. 1985; see also reviews by ACGIH 2014; EPA 2016a; IARC 2017). 1,2-Dichloropropane is also a CNS depressant in animals exposed to inhalation concentrations ≥500 ppm and oral doses ≥100 mg/kg/day (Bruckner et al. 1989; Exxon 1981a; Gorzinski and Johnson 1989; Heppel et al. 1946b; Kirk et al. 1989; Nitschke and Johnson 1983; Shell Oil Co. 1982). Effects were generally transient unless observed at high exposure levels associated with lethality.

Developmental Effects. No human studies evaluating developmental toxicity were identified. In oral exposure studies in animals, delayed skull ossification was observed in rat and rabbit fetuses at gestational exposure doses ≥125 mg/kg/day, but findings may be secondary to maternal toxicity (clinical signs, decreased body weight) observed at the same dose in both species (Kirk et al. 1995). Similarly, decreased neonatal survival and reduced neonatal body weights were observed in a 2-generation study at drinking water exposure levels of 152–254 mg/kg/day, which corresponded to parental toxicity

(decreased body weight, maternal anemia, hepatic toxicity) (Kirk et al. 1990). No inhalation studies in laboratory animals were identified.

Cancer. A series of case reports and retrospective cohort studies from Japanese printing companies indicate that exposure to high air levels of 1,2-dichloropropane (and/or other chlorinated solvents) may increase the risk of developing cholangiocarcinoma (CCA), a rare form of bile duct cancer (Kinoshita et al. 2019; Kubo et al. 2013, 2014a, 2014b; Kumagai 2014; Kumagai et al. 2013, 2014, 2016; Nakagawa et al. 2015; Ogawa et al. 2020; Sobue et al. 2015; Tomimaru et al. 2015; Yamada et al. 2014, 2015a, 2015b). Actual air levels of chlorinated solvents were not measured, but based on quantities of chemicals reportedly used, some studies estimated that print shop workers were exposed to 1,2-dichloropropane at concentrations ranging from 7 to 346 ppm (Kumagai et al. 2013, 2016; Yamada et al. 2014, 2015a, 2015b). Most workers were also exposed to other chlorinated solvents, including dichloromethane (15–360 ppm) and/or 1,1,1-trichloroethane (exposure levels not estimated). An excess of CCA has also been associated with employment in the printing and printing-related industries in Nordic and European countries; however, it is unclear if 1,2-dichloropropane was used in print shops in these countries (Ahrens et al. 2014; Vlaanderen et al. 2013).

1,2-Dichloropropane is carcinogenic in laboratory animals following both inhalation and oral exposure. There is evidence for respiratory tract cancer following inhalation exposure (nasal tumors in rats, lung tumors in mice) and some evidence for neoplastic lesions in the Harderian gland and spleen in male mice (Matsumoto et al. 2013; Umeda et al. 2010). Following oral exposure, the NTP (1986) concluded that there was equivocal evidence of mammary tumors in female rats and some evidence of liver tumors in male and female mice.

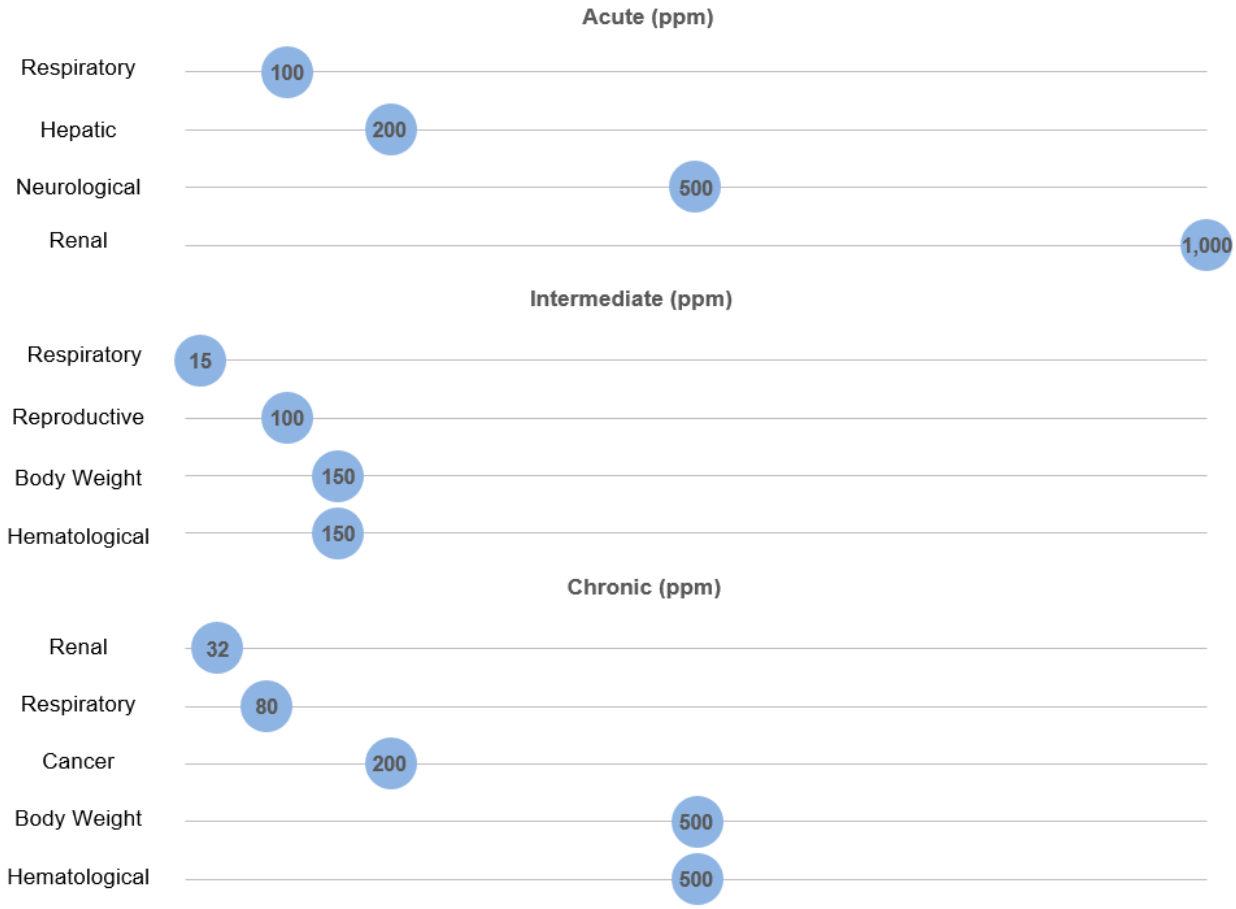
The International Agency for Research on Cancer (IARC 2017) concluded that 1,2-dichloropropane is carcinogenic to humans (Group 1) based on evidence that 1,2-dichloropropane exposure causes cancer of the biliary tract (CCA) in occupationally exposed workers and supporting mechanistic data. The EPA Peer-Reviewed Provisional Toxicity Value (PPRTV) program determined that 1,2-dichloropropane is likely to be carcinogenic to humans based on evidence of a potential correlation between occupational exposure to 1,2-dichloropropane and CCA cancer and adequate evidence in laboratory animals (EPA 2016a).

1.3 MINIMAL RISK LEVELS (MRLs)

The inhalation database was considered adequate for deriving acute- and intermediate-duration MRLs but inadequate for derivation of a chronic-duration MRL. As presented in Figure 1-3, the available inhalation data for 1,2-dichloropropane suggest that the upper respiratory tract is the most sensitive target of toxicity in laboratory animals.

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

The upper respiratory system is the most sensitive target of 1,2-dichloropropane.
Numbers in circles are the lowest LOAELs for all health effects in animals; no reliable dose-response data were available for humans.

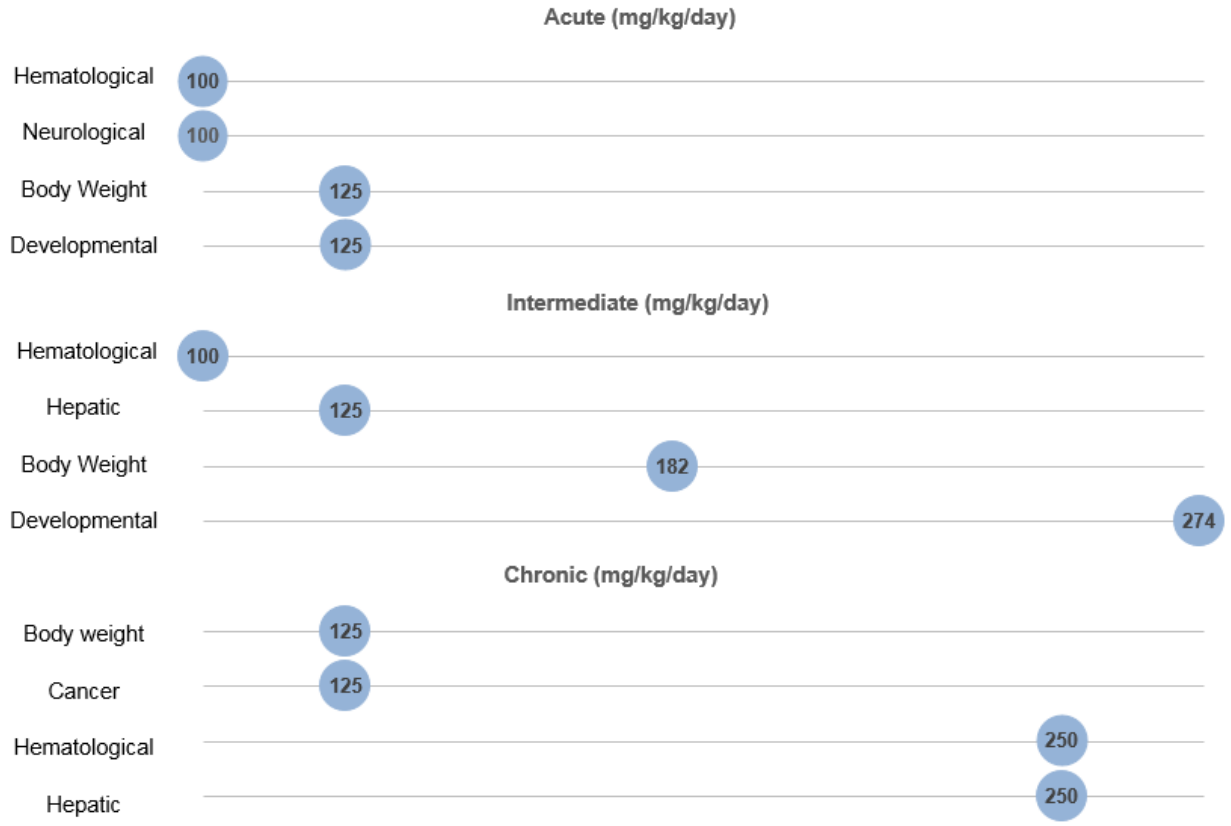


The oral database was considered adequate for deriving acute- and intermediate-duration MRLs. The oral database was inadequate for derivation of a chronic-duration MRL. As presented in Figure 1-4, the available oral data for 1,2-dichloropropane suggest that the CNS, liver, hematological system, developing fetus, and cancer are the most sensitive targets of toxicity in laboratory animals.

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

The CNS, liver, hematological system, developing fetus, and cancer are the most sensitive targets of 1,2-dichloropropane.

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 are summarized in Table 1-1 and discussed in greater detail in Appendix A.

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

Exposure duration	MRL	Critical effect	Point of departure/ human equivalent concentration	Uncertainty factor	Reference
Inhalation exposure (ppm)					
Acute	0.02	Slight degeneration of the olfactory mucosa in rats	LOAEL: 100 ($LOAEL_{HEC}$: 1.8)	90	Nitschke and Johnson 1983
Intermediate	0.002	Very slight hyperplasia of the nasal respiratory epithelium in rats	$BMCL_{10}$: 2.38 ($BMCL_{10[HEC]}$:0.05)	30	Nitschke et al. 1988
Chronic	Insufficient data for MRL derivation				
Oral exposure (mg/kg/day)					
Acute	0.3	Maternal anemia in rabbits	$BMDL_{1SD}$: 30	100	Berdasco et al. 1988; Kirk et al. 1995
Intermediate	0.07	Hemolytic anemia in rats	LOAEL: 100 $LOAEL_{ADJ}$: 71	1,000	Bruckner et al. 1989
Chronic	Insufficient data for MRL derivation				

[a]See Appendix A for additional information.

ADJ = adjusted for continuous exposure; BMDL/BMCL= 95% lower confidence limit on the benchmark dose/concentration (subscripts denote benchmark response: exposure level associated with 10% extra risk or 1 SD change in endpoint); HEC = human equivalency concentration; LOAEL = lowest-observed-adverse-effect level; SD = standard deviation

CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of 1,2-dichloropropane. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health. When available, mechanisms of action are discussed along with the health effects data; toxicokinetic mechanistic data are discussed in Section 3.1.

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

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized by health effect. These data are discussed in terms of route of exposure (inhalation, oral, and dermal) and three exposure periods: acute (≤14 days), intermediate (15–364 days), and chronic (≥365 days).

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figure 2-1 provides an overview of the database of studies in humans or experimental animals included in this chapter of the profile. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to 1,2-dichloropropane, 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 1,2-dichloropropane 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, animal oral studies are presented in Table 2-2 and Figure 2-3, and animal dermal studies are presented in Table 2-3. Summaries of human observational cancer studies are presented in Table 2-4 in Section 2.19 (Cancer).

Levels of significant exposure (LSEs) for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects (SLOAELs) are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant

dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an endpoint should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these endpoints. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is 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 1,2-dichloropropane are indicated in Tables 2-1 and 2-2 and Figures 2-2 and 2-3.

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

The health effects of 1,2-dichloropropane have been evaluated in a limited number of epidemiology studies and several animal studies. As illustrated in Figure 2-1, the most widely examined endpoints were hepatic, renal, hematological, and body weight effects. Most available health effects data come from oral and inhalation exposure studies in animals. Animal data are available for each health effect category and exposure duration category. The small number of available observational epidemiology studies were predominantly focused on cancer, with one case-control study evaluating potential associations with atopic dermatitis. Additional information comes from several case reports of acute oral or inhalation poisoning.

The human and animal studies suggest several sensitive targets of 1,2-dichloropropane toxicity:

- **Respiratory Endpoints.** Respiratory effects are a presumed health effect for humans based on limited evidence of respiratory tract irritation in humans and strong evidence of nasal lesions in laboratory animals following acute-, intermediate-, and chronic-duration inhalation exposure. Acute exposures resulted in degeneration of the olfactory mucosa and inflammatory and exudative changes in rats, with mice and rabbits showing nasal mucosal degeneration to a lesser degree. Nasal lesions observed after intermediate-duration exposure included inflammation and hyperplasia of the respiratory epithelium, degeneration and atrophy of the olfactory epithelium, and submucosal inflammation in rats; metaplasia, atrophy, necrosis, and desquamation of the respiratory epithelium in mice; and slight degeneration of the olfactory epithelium in rabbits. Following chronic-duration exposure, nasal lesions observed in rats and mice included inflammation and metaplasia of the respiratory epithelium, hyperplasia of the transitional

epithelium, atrophy of the olfactory epithelium, and squamous cell hyperplasia of the submucosal glands.

- **Hematological Endpoints.** Hematological effects are a presumed health effect for humans based on limited evidence in humans and strong evidence of hemolytic anemia in laboratory animals following inhalation and oral exposure. Human findings include case reports of hemolytic anemia and disseminated intravascular coagulation following acute inhalation, oral, or dermal exposure. Hemolytic anemia in animals was characterized by increased serum bilirubin levels, bone marrow congestion, hemosiderosis in the spleen, and/or increased hematopoiesis in the spleen and bone marrow following acute- or intermediate-duration inhalation and oral exposures. However, only mild anemia was observed following chronic-duration inhalation exposure. Hematological blood parameters were not assessed following chronic-duration oral exposure.

- **Hepatic Endpoints.** Hepatic effects are a presumed health effect for humans based on limited evidence in humans and strong evidence from inhalation and oral studies in animals. Numerous human cases studies report hepatic effects, including altered serum liver enzymes, impaired liver function, toxic hepatitis, hepatic necrosis, and liver failure, following acute inhalation, oral, or dermal exposure to high exposure levels of 1,2-dichloropropane. Hepatic lesions, primarily fatty degeneration and necrosis, were consistently observed in inhalation and oral studies in laboratory animals.

- **Neurological Endpoints.** CNS depression is a presumed health effect for humans based on limited evidence in humans, limited evidence in laboratory animals following acute inhalation exposure, and strong evidence in laboratory animals following acute oral exposure.

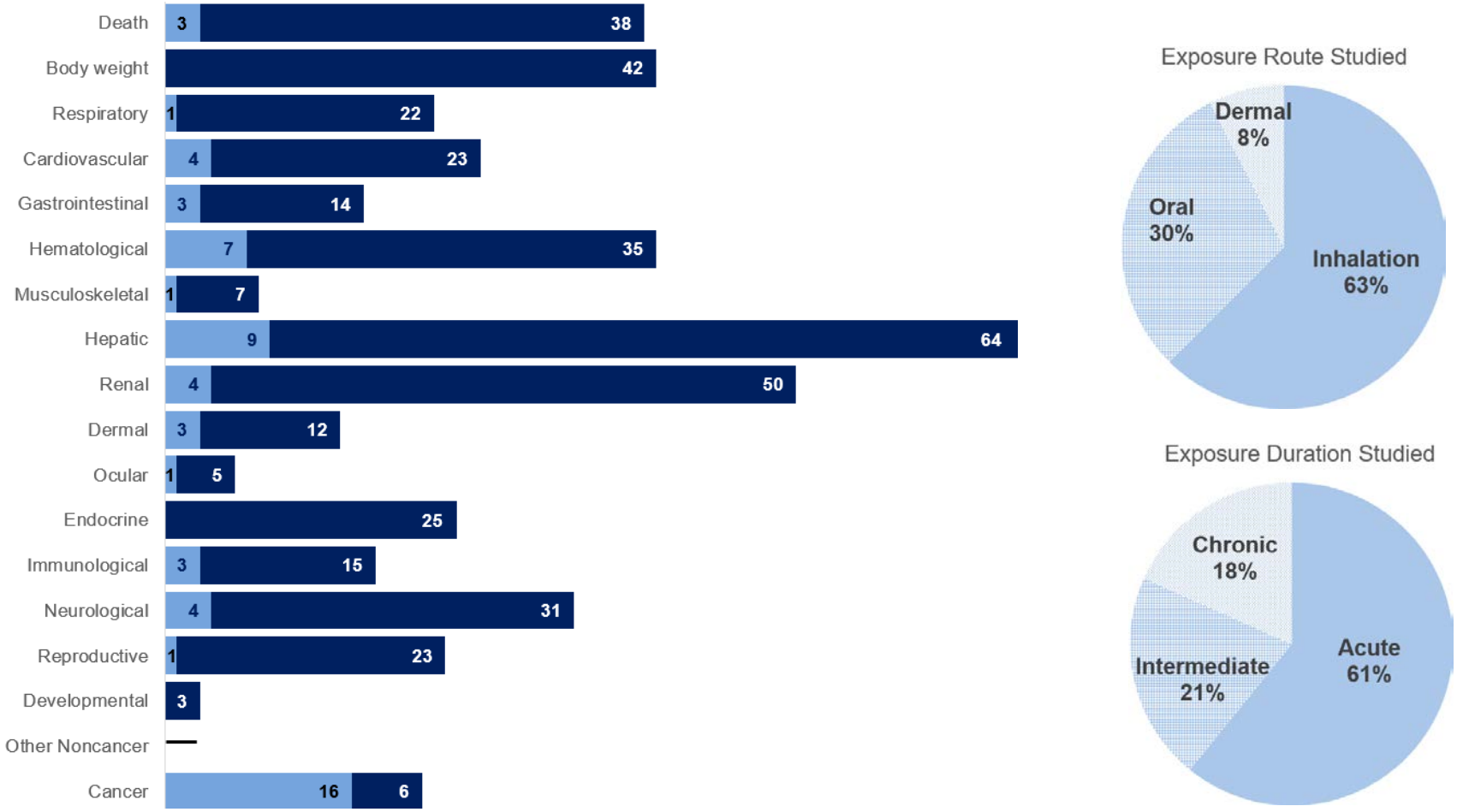
- **Developmental Endpoints.** Developmental toxicity is a presumed effect for humans based on high evidence of developmental effects (delayed skeletal development, decreased neonatal weight and survival) in laboratory animals at high oral doses. Maternal toxicity (decreased maternal body weight, maternal CNS depression) was observed at similar doses.

- **Renal Endpoints.** Available data are inadequate to determine if renal effects will occur in humans following exposure to 1,2-dichloropropane. A few human case reports indicate renal failure following oral or inhalation exposure to high levels of 1,2-dichloropropane. In laboratory animals, there is inconsistent evidence for renal lesions following inhalation exposure and no evidence of renal toxicity following oral exposure.

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

Hepatic, renal, hematological, and body weight effects of 1,2-dichloropropane were the most widely examined potential toxicity outcomes

More studies evaluated health effects in **animals** than **humans** (counts represent studies examining endpoint)



*Includes studies discussed in Chapter 2. A total of 113 studies (including those finding no effect) have examined toxicity; most animal studies examined multiple endpoints.

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

Figure key[a]	Species (strain) No./group	Exposure scenario	Concentrations (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
ACUTE EXPOSURE									
1	Rat (Sherman) 6 NS	4 hours (WB)	2,000	LE	Death			2,000	2–4/6 died (exact number not reported)
Carpenter et al. 1949									
2	Rat (NS) 12 B	7 hours (WB)	1,600	CS, LE	Death			1,600	3/12 died
					Neuro		1,600		Mild incoordination
Heppel et al. 1946a									
3	Rat (NS) 13–20 B	5–8 days 7 hours/day (WB)	1,600, 2,200	CS, LE	Death			2,200	8/20 died
					Bd wt		1,600		Body weight loss
					Resp		2,200		Lung congestion
					Cardio	2,200			
					Hepatic		2,200		Fatty degeneration, centrilobular congestion, necrosis
					Endocr		2,200		Lipoid depletion in adrenal cortex
					Neuro		1,600	2,200	Mild incoordination at 1,600 ppm, with gross incoordination and prostration at 2,200 ppm
Heppel et al. 1946b [Histology assessed at 2,200 ppm only]									
4	Rat (NS) 3–8 NS	3–12 days 7 hours/day (WB)	0, 400	LE, HP	Cardio	400			
					Hepatic	400			
					Renal	400			
Heppel et al. 1948									
5	Rat (Sprague-Dawley) 33 NS; 3 controls	7 hours (WB)	0, 2,200	GN, HP, CS	Death			2,200	2/33 died
					Hepatic		2,200		Fatty degeneration, centrilobular necrosis
					Renal		2,200		Fatty degeneration
					Endocr		2,200		Depletion of the lipoid material of the adrenal cortex
Highman and Heppel 1946									

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

Figure key[a]	Species (strain) No./group	Exposure scenario	Concentrations (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
6	Rat (Sprague-Dawley) 36 NS, 6 controls	1–5 days 7 hours/day (WB)	0, 2,200	GN, HP, CS	Death			2,200	9/36 died
					Hepatic		2,200		Fatty degeneration, centrilobular necrosis
					Renal		2,200		Fatty degeneration
					Endocr		2,200		Depletion of the lipoid material of the adrenal cortex
Highman and Heppel 1946									
7	Rat (NS) NS	4 hours (NS)	2,000	LE	Death			2,000	Approximate lethal concentration (ALC)
Kennedy and Graepel 1991									
8	Rat (Fischer-344) 5 M	6 hours (WB)	0, 500, 1,500	CS, HP	Hepatic	1,500			
					Renal	1,500			
					Neuro	500		1,500	Anesthesia
Nitschke and Johnson 1983									
9	Rat (Fischer-344) 5 M, 5 F	2 weeks 4–5 days/week 6 hours/day (WB)	0, 100, 300, 1,000	BC, BI, BW, CS, GN, HE, HP, OW, UR	Resp		100[b]		Olfactory mucosal degeneration
					Hemato	1,000			
					Hepatic	300	1,000		Increased liver weight, hepatocellular hypertrophy in females
					Renal	1,000			
					Endocr	1,000			No histopathological lesions in adrenal glands
					Repro	1,000 M			No histopathological lesions in testes
Nitschke and Johnson 1983									
10	Rat (NS) 6 NS	8 hours (NS)	2,000	LE	Death			2,000	LC_{50}
Smyth et al. 1969									

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

Figure key[a]	Species (strain) No./group	Exposure scenario	Concentrations (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
11	Rat (Fischer-344) 3 NS	7 days 8 hours/day (WB)	0, 300, 1,000, 3,000	BI, LE, HP	Hepatic	1,000	3,000		Fat-droplets
Zhang et al. 2015									
12	Mouse	10 hours (NS)	300, 380, 390, 700, 715, 1,625	BC, CS	Death			480	LC_{50}
Dow Chemical Co. 1968									
13	Mouse (NS) 10–26 B	2–7 hours (WB)	1,000, 1,500, 2,200	CS, LE, HP	Death			1,000	100% mortality
					Hepatic		1,000		Fatty degeneration and centrilobular vacuolation and congestion at ≥1,000 ppm, necrosis at 2,200 ppm
					Renal		1,000		Fatty degeneration
					Neuro			2,200	Gross motor incoordination followed by prostration (effects at 1,000 ppm not reported)
Heppel et al. 1946a									
14	Mouse (C57BL/6N) 5–18 (NS)	1–12 days 7 hours/day (WB)	0, 400	LE, HP	Death			400	8/18 died after one exposure
					Hepatic		400		Slight fatty degeneration
Heppel et al. 1948									
15	Mouse (B6C3F1) 5 M	6 hours (WB)	0, 500, 1,500	CS, LE, HP	Death			500	2/5 died at 500 ppm; 5/5 died at 1,500 ppm
					Bd wt	500			
					Hepatic			500	Hemorrhagic necrosis
					Renal	1500			
					Neuro			500	Lethargy at 500 ppm, anesthesia at 1,500 ppm
Nitschke and Johnson 1983									

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

Figure key[a]	Species (strain) No./group	Exposure scenario	Concentrations (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
16	Mouse (B6C3F1) 5 M, 5 F	2 weeks 4–5 days/week 6 hours/day (WB)	0, 30, 100, 300	BC, BW, CS, GN, HE, HP, OW	Bd wt	300			
					Resp	100	300		Olfactory mucosal degeneration
					Hemato	300			
					Hepatic	100	300		Increased liver weight, hepatocellular hypertrophy, vacuolization
					Renal	300			
					Endocr	300			No histological changes in adrenal glands
					Immuno	100	300		Decreased thymus weight, decreased lymphoid cells
					Repro	300 M			No histological changes in testes
Nitschke and Johnson 1983									
17	Mouse (C57BL/6J) NS M	2 days 3–6 hours/day (WB)	0, 100, 200, 400	BC, OW	Hepatic	400			
Toyooka et al. 2017									
18	Mouse (B6C3F1) 5–6 M	1–4 hours (WB)	0, 300	BW, BC, OW, HP	Bd wt	300			
					Hepatic	300			
Wang et al. 2019									
19	Mouse (B6C3F1) 5–6 M	6 hours (WB)	0, 300	BW, BC, OW, HP	Bd wt	300			
					Hepatic		300		9–12% increase in liver weight; increased ALT and AST; hepatocellular hypertrophy, necrosis, and granular degeneration
Wang et al. 2019									

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

Figure key[a]	Species (strain) No./group	Exposure scenario	Concentrations (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
20	Mouse (BALB/cA) 3 NS	7 days 8 hours/day (WB)	0, 300, 1,000, 3,000	BI, LE, HP	Death			1,000	100% mortality
					Hepatic		300		Vacuolization
Zhang et al. 2015									
21	Mouse (C57BL/6J) 3 NS	7 days 8 hours/day (WB)	0, 300, 1,000, 3,000	BI, LE, HP	Death			1,000	100% mortality
					Hepatic		300		Vacuolization
Zhang et al. 2015									
22	Mouse (BALB/cA) 8 NS	14 days 6 hours/day (WB)	0, 200, 400, 800	BI, BW, LE, OW, HP	Death			400	100% mortality
					Hepatic		200		Vacuolization
Zhang et al. 2015									
23	Guinea pig (NS) 10–16 B	5 days 7 hours/day (WB)	1,600, 2,200	CS, HP, LE	Death			2,200	11/16 died
					Bd wt		1,600		Body weight loss
					Resp		2,200		Lung congestion
					Cardio	2,200			
					Hepatic		2,200		Fatty degeneration, centrilobular congestion, necrosis
					Renal		2,200		Fatty degeneration
					Ocular	1,600	2,200		Conjunctivitis
					Endocr		2,200		Adrenal necrosis
					Neuro	1,600	2,200		Listlessness
Heppel et al. 1946a [Histology assessed at 2,200 ppm only]									
24	Guinea pig (NS) 4 NS	1–4 days 7 hours/day (WB)	0, 400	LE, HP	Cardio	400			
					Hepatic	400			
					Renal	400			
Heppel et al. 1948									

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

Figure key[a]	Species (strain) No./group	Exposure scenario	Concentrations (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
25	Guinea pig (NS) 33 NS; 3 controls	7 hours (WB)	0, 2,200	GN, HP, CS	Hepatic		2,200		Fatty degeneration, centrilobular swelling
					Renal		2,200		Fatty degeneration
					Endocr		2,200		Adrenal necrosis
Highman and Heppel 1946									
26	Guinea pig (NS) 30 NS; 6 controls	2–3 days 4 or 7 hours/day (WB)	0, 2,200	GN, HP, CS	Death			2,200	7/30 died
Highman and Heppel 1946									
27	Guinea pig (NS) 3 NS	7 days 8 hours/day (WB)	0, 300, 1,000, 3,000	BI, LE, HP	Death			3,000	100% mortality
					Hepatic	1,000			
Zhang et al. 2015									
28	Hamster (Golden Syrian) 3 NS	7 days 8 hours/day (WB)	0, 300, 1,000, 3,000	BI, LE, HP	Death			1,000	100% mortality
					Hepatic	300			
Zhang et al. 2015									
29	Hamster (Golden Syrian) 8 NS	14 days 6 hours/day (WB)	0, 200, 400, 800	BI, BW, LE, OW, HP	Death			800	100% mortality
					Hepatic	200	400		Slight dilatation of hepatic sinusoids
Zhang et al. 2015									
30	Rabbit (NS) 2–4 NS	2–8 days 7 hours/day (WB)	1,600, 2,200	CS, HP, LE	Death			1,600	1/2 died at 1,600 ppm; 2/4 died at 2,200 ppm
					Cardio	2,200			
					Hepatic		1,600		Fatty degeneration
					Renal		1,600		Fatty degeneration
Heppel et al. 1946a									

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

Figure key[a]	Species (strain) No./group	Exposure scenario	Concentrations (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
31	Rabbit (New Zealand) 5 M	2 weeks 4–5 days/week 6 hours/day (WB)	0, 100, 300, 1,000	BC, BW, CS, GN, HP, OW	Bd wt	1,000			
					Resp	300	1,000		Olfactory mucosal degeneration
					Hepatic	1,000			
					Renal	1,000			
					Endocr	1,000			No histopathological changes in adrenal glands
					Immuno	1,000			No histopathological changes in thymus or bone marrow
					Repro	1,000			No histopathological changes in testes
Nitschke and Johnson 1983									
INTERMEDIATE EXPOSURE									
32	Rat (Wistar) 10–12 NS	15 days 7 hours/day; 1,000, 1,500 (WB)	1,500	LE	Death			1,500	3/12 died
Heppel et al. 1946b									
33	Rat (Wistar, Sprague-Dawley) 18–51 B	35–97 days 7 hours/day 5 days/week (WB)	0, 1,000, 1,500	CS, BW, HP, LE	Death			1,000	25/45 died at 1,000 ppm; 8/18 died at 1,500 ppm
					Bd wt		1,000		Decreased body weight gain
					Cardio	1,500			
					Hepatic	1,000	1,500		Slight centrilobular fatty degeneration
					Renal	1,500			
					Neuro		1,000		Mild incoordination and weakness
Heppel et al. 1946a									

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

Figure key[a]	Species (strain) No./group	Exposure scenario	Concentrations (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
34	Rat (NS) 19–26 M, 10–23 F	Up to 28 weeks 5 days/week 7 hours/day (WB)	0, 400	BW, LE, HP	Bd wt	400			
					Cardio	400			
					Hepatic	400			
					Renal	400			
Heppel et al. 1948									
35	Rat (Fischer-344) 10 M, 10 F	13 weeks 5 days/week 6 hours/day (WB)	0, 15, 50, 150	BW, OW, GN, HP, BC, CS, UR, HE	Bd wt	50 M 150 F	150 M		10% decrease in body weight
					Resp		15[c]		Hyperplasia of the nasal respiratory epithelium at ≥15 ppm; degeneration of the olfactory mucosa at ≥50 ppm; submucosal inflammation in males at 150 ppm. $BMCL_{10}$=2.38 ppm.
					Cardio	150			
					Gastro	150			
					Hemato	150			
					Musc/skel	150			
					Hepatic	150			
					Renal	150			
					Dermal	150			
					Ocular	150			
					Endocr	150			
					Immuno	150			
					Neuro	150			
					Repro	150			
Nitschke et al. 1988									
36	Rat (Fischer-344) 6–9 F	21–24 days 8 hours/day (WB)	0, 50, 100, 200	BW, OW, RX	Bd wt	200			
					Repro	50	100		Lengthened estrous cycle at ≥100 ppm; decreased ovulation at 200 ppm
Sekiguchi et al. 2002									

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

Figure key[a]	Species (strain) No./group	Exposure scenario	Concentrations (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
37	Rat (F344/DuCrj) 10 M, 10 F	13 weeks 5 days/week 6 hours/day (WB)	0, 125, 250, 500, 1,000, 2,000	BC, BW, CS, FI, GN, HE, HP, OW	Bd wt	500	1,000		>10% decrease in body weight
					Resp		125		Hyperplasia of respiratory epithelium, atrophy of olfactory epithelium at ≥125 ppm; inflammation of respiratory epithelium at ≥1,000 ppm
					Cardio	2,000			
					Gastro	2,000			
					Hemato	250	500		Hemolytic anemia, hemosiderosis in the spleen, increased hematopoiesis in the spleen and bone marrow
					Hepatic	1,000	2,000		Centrilobular hepatocyte swelling, increased liver weight in females
					Renal	2,000			
					Endocr	1,000 F 2,000 M	2,000 F		Fatty change in adrenal glands
					Neuro	2,000			
					Repro	2,000			
Umeda et al. 2010									
38	Mouse (C3H) 80 (NS)	37 days 4–7 hours/day (WB)	0, 400	LE, HP	Death			400	96% mortality
					Hepatic		400		Fatty degeneration, centrilobular congestion, necrosis
					Renal		400		Fatty degeneration
Heppel et al. 1948									
39	Mouse (B6D2F1/Crlj) 10 M, 10 F	13 weeks 5 days/week 6 hours/day (WB)	0, 50, 100, 200, 300, 400	BC, BW, CS, FI, GN, HE, HP, OW	Death			300 M	2/10 died at 300 ppm; 6/10 died at 400 ppm
					Bd wt	200 M 400 F	300 M		>10% decrease in body weight in males
					Resp	200	300		Respiratory metaplasia, atrophy, necrosis, and desquamation of nasal cavity
					Cardio	300	400		"Ground glass" appearance

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

Figure key[a]	Species (strain) No./group	Exposure scenario	Concentrations (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
					Gastro	300	400		Forestomach hyperplasia
					Hemato	200	300		Hemolytic anemia, increased extramedullary hematopoiesis and hemosiderin deposits in the spleen, and bone marrow congestion
					Hepatic	200	300		Increased liver weight and centrilobular hepatocyte swelling at ≥300 ppm; fatty and vacuolic changes and necrosis at 400 ppm
					Renal	400			
					Endocr	400			
					Neuro	400			
					Repro	400			
Matsumoto et al. 2013									
40	Mouse (B6C3F1) 10 M,10 F	13 weeks 5 days/week 6 hours/day (WB)	0, 15, 50, 150	BW, OW, GN, HP, CS, HE	Bd wt	150			
					Resp	150			
					Cardio	150			
					Gastro	150			
					Hemato	150			
					Musc/skel	150			
					Hepatic	150			
					Renal	150			
					Dermal	150			
					Ocular	150			
					Endocr	150			
					Immuno	150			
					Neuro	150			
					Repro	150			
Nitschke et al. 1988									

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

Figure key[a]	Species (strain) No./group	Exposure scenario	Concentrations (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
41	Mouse (C57Bl/6JJcl) 6 M	4 weeks 8 hours/day 7 days/week (WB)	0, 50, 250	BW, BC, BI, LE, OW, HP	Bd wt	250			
					Hepatic	50	250		Increased ALT and bilirubin; increased liver weight; focal necrosis and bile duct hyperplasia
Zhang et al. 2018									
42	Guinea pig (NS) 12–39 B	39–126 days 7 hours/day 5 days/week (WB)	0, 1,000, 1,500	BW, CS, HP, LE	Death			1,000	3/12 died at 1,000 ppm, 5/18 died at 1,500 ppm
					Bd wt		1,000		Decreased body weight gain
					Cardio	1,500			
					Hepatic	1,000	1,500		Fatty degeneration, centrilobular congestion and necrosis
					Renal	1,000	1,500		Fatty degeneration
					Endocr		1,000		Subcortical fibrosis of the adrenal glands at ≥1,000 ppm, adrenal cortex necrosis at 1,500 ppm
					Neuro		1,000		Transient CNS depression
Heppel et al. 1946a									
43	Guinea pig (NS) 16–24 B	Up to 27 weeks 5 days/week 7 hours/day (WB)	0, 400	BW, LE, HP	Bd wt	400			
					Hepatic		400		Slight fatty degeneration
					Renal		400		Slight fatty degeneration
Heppel et al. 1948									
44	Dog (NS) 1–5 F	55–128 days 7 hours/day 5 days/week (WB)	0, 1,000	CS, LE, OF, HP	Death			1,000	5/9 died (severe anorexia noted)
					Cardio		1,000		Fatty degeneration
					Hemato	1,000			
					Hepatic		1,000		Fatty degeneration
					Renal		1,000		Fatty degeneration
					Endocr		1,000		Lipoid depletion of adrenal glands, atrophy and necrosis of adrenal cortex
Heppel et al. 1946a									

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

Figure key[a]	Species (strain) No./group	Exposure scenario	Concentrations (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
45	Dog (NS) 5 NS	26 weeks 5 days/week 7 hours/day (WB)	0, 400	BW, LE, HP	Bd wt	400			
					Cardio	400			
					Hepatic	400			
					Renal	400			
Heppel et al. 1948									
46	Rabbit (NS) 4–8 B	39–126 days 7 hours/day 5 days/week (WB)	0, 1,000, 1,500	BW, CS, HE, HP, LE	Death			1,500	1/4 died
					Bd wt	1,500			
					Cardio	1,500			
					Hemato	1,500			
					Hepatic	1,500			
					Renal	1,500			
Heppel et al. 1946a									
47	Rabbit (New Zealand) 7 M, 7 F	13 weeks 5 days/week 6 hours/day (WB)	0, 150, 500, 1,000	BW, OW, GN HP, BC, HE,	Bd wt	1,000			
					Resp	500	1,000		Olfactory epithelium degeneration of nasal cavity
					Cardio	1,000			
					Gastro	1,000			
					Hemato		150		Anemia at ≥150 ppm; bone marrow hyperplasia at ≥500 ppm
					Musc/skel	1,000			
					Hepatic	1,000			
					Renal	1,000			
					Dermal	1,000			
					Ocular	1,000			
					Endocr	1,000			
					Immuno	1,000			
					Neuro	1,000			
					Repro	1,000			
Nitschke et al. 1988									

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

Figure key[a]	Species (strain) No./group	Exposure scenario	Concentrations (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
CHRONIC EXPOSURE									
48	Rat (F344/DuCrj) 50 M, 50 F	104 weeks 5 days/week 6 hours/day (WB)	0, 80, 200, 500	BC, BW, CS, FI, GN, HE, HP, OW	Bd wt	200	500		8–11% decrease in body weight
					Resp		80		Atrophy of olfactory epithelium, inflammation and squamous cell metaplasia of respiratory epithelium, and hyperplasia of the transitional epithelium at ≥80 ppm; squamous cell hyperplasia and hyperplasia of the submucosal glands at ≥200 ppm
					Cardio	500			
					Gastro	500			
					Hemato	200 F 500 M	500 F		Mild anemia
					Hepatic	500			
					Renal	500			
					Endocr	500			
					Immuno	500			
					Neuro	500			
					Repro	500			
					Cancer			500	CEL: nasal papillomas
Umeda et al. 2010									
49	Mouse (B6D2F1/Crlj) 50 M, 50 F	104 weeks 5 days/week 6 hours/day (WB)	0, 32, 80, 200	BC, BW, CS, FI, GN, HE, HP, OW	Bd wt	200			
					Resp	32	80		Atrophy of olfactory epithelium at ≥80 ppm; metaplasia of the olfactory epithelium and submucosal glands at 200 ppm
					Cardio	200			
					Gastro	200			
					Hemato	200			
					Hepatic	200			

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

Figure key[a]	Species (strain) No./group	Exposure scenario	Concentrations (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
					Renal	200 F			
							32 M		Increased kidney weight, basophilic changes, and cortical mineralization
					Endocr	200			
					Immuno	200			
					Neuro	200			
					Cancer			200	CEL: bronchioloalveolar adenoma or carcinoma in males and females; Harderian gland adenomas and hemangioma/ hemangiosarcoma in spleen in males
Matsumoto et al. 2013									

[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 acute-duration inhalation minimal risk level (MRL). The LOAEL of 100 ppm was adjusted for continuous exposure and converted into a human equivalent concentration (HEC) of 1.8 ppm, and divided by and uncertainty factor of 90 (3 for use of a minimal LOAEL, 3 for animal to human with dosimetric adjustments, and 10 for human variability), resulting in an MRL of 0.02 ppm
[c]Use to derive an intermediate-duration inhalation MRL. Using benchmark dose modeling, BMC_{10} and $BMCL_{10}$ values of 6.76 and 2.38 ppm, respectively, were calculated for nasal respiratory epithelium hyperplasia in male and female rats. The $BMDL_{10}$ was adjusted for continuous exposure and converted into a HEC of 0.05 ppm divided by an uncertainty factor of 30 (3 for animal to human with dosimetric adjustments and 10 for human variability), resulting in an MRL of 0.002 ppm.

Principal studies for the MRLs

ALT = alanine aminotransferase; AST = aspartate aminotransferase; B = both sexes; BC = serum (blood) chemistry; Bd Wt or BW = body weight; BI = biochemical changes; BMC = benchmark concentration; BMCL= 95% lower confidence limit on the benchmark concentration (subscripts denote benchmark response: exposure level associated with 10% extra risk or 1 standard deviation change in endpoint); Cardio = cardiovascular; CEL = cancer effect level; CNS = central nervous system; CS = clinical signs; Endocr = endocrine; F = female(s); FI = food intake; Gastro = gastrointestinal; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; LE = lethality; LC_{50} = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male(s); Musc/skel = musculoskeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OF = organ function; OW = organ weight; Repro = reproductive; Resp = respiratory; UR = urinalysis; WB = whole body

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

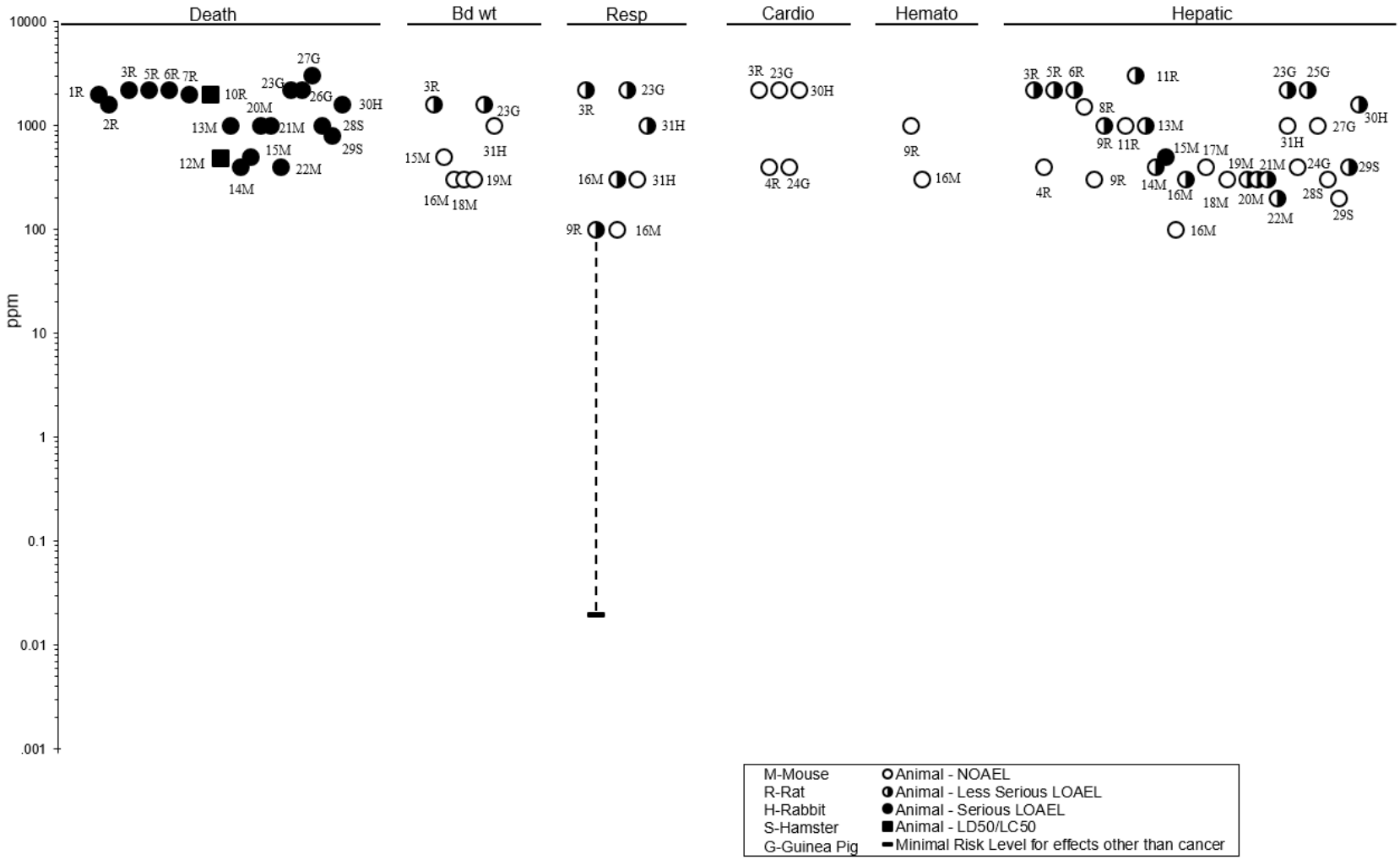


Figure 2-2. Levels of Significant Exposure to 1,2-Dichloropropane – Inhalation
Acute (≤ 14 days)

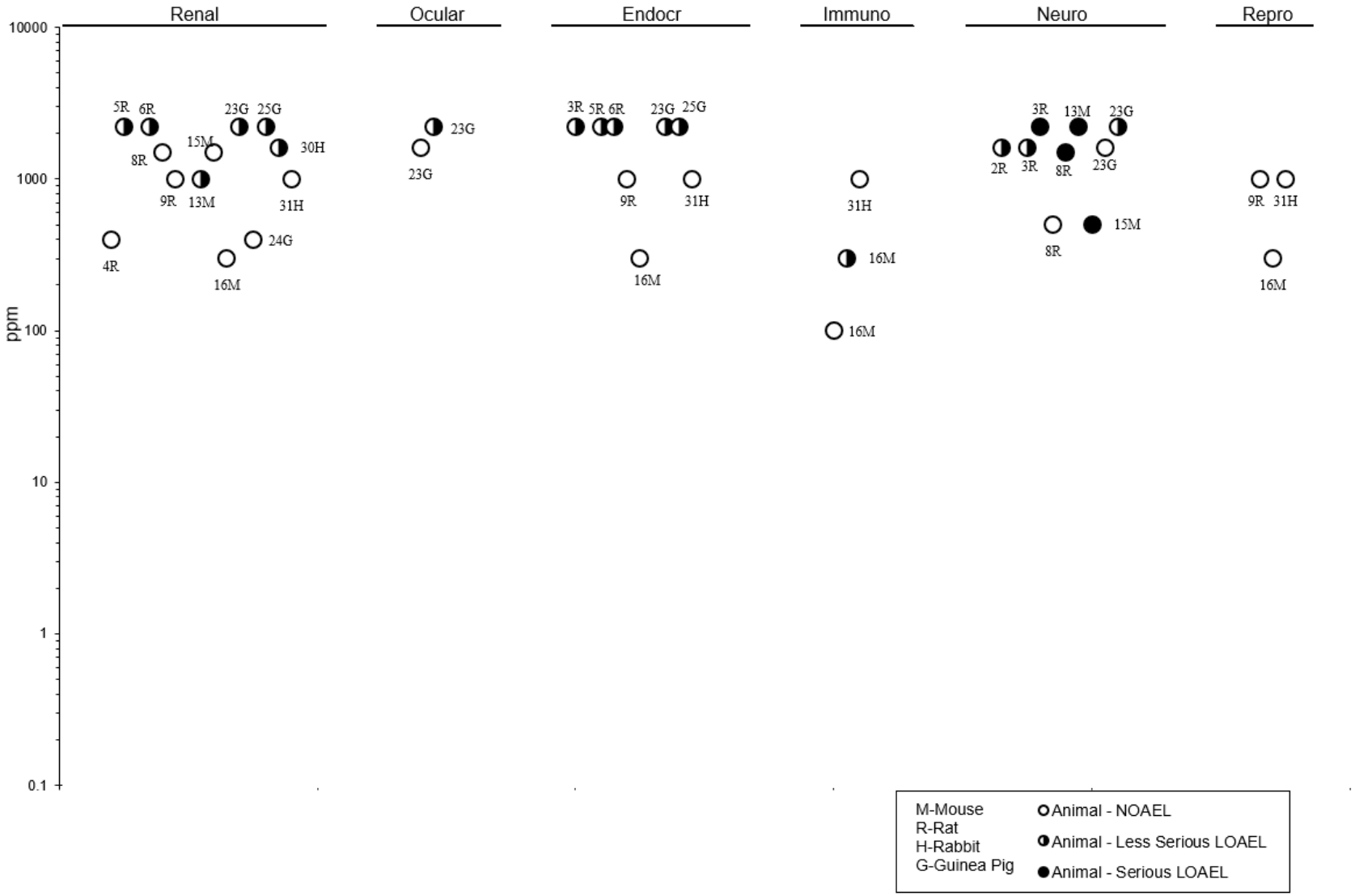


Figure 2-2. Levels of Significant Exposure to 1,2-Dichloropropane – Inhalation
Intermediate (15-364 days)

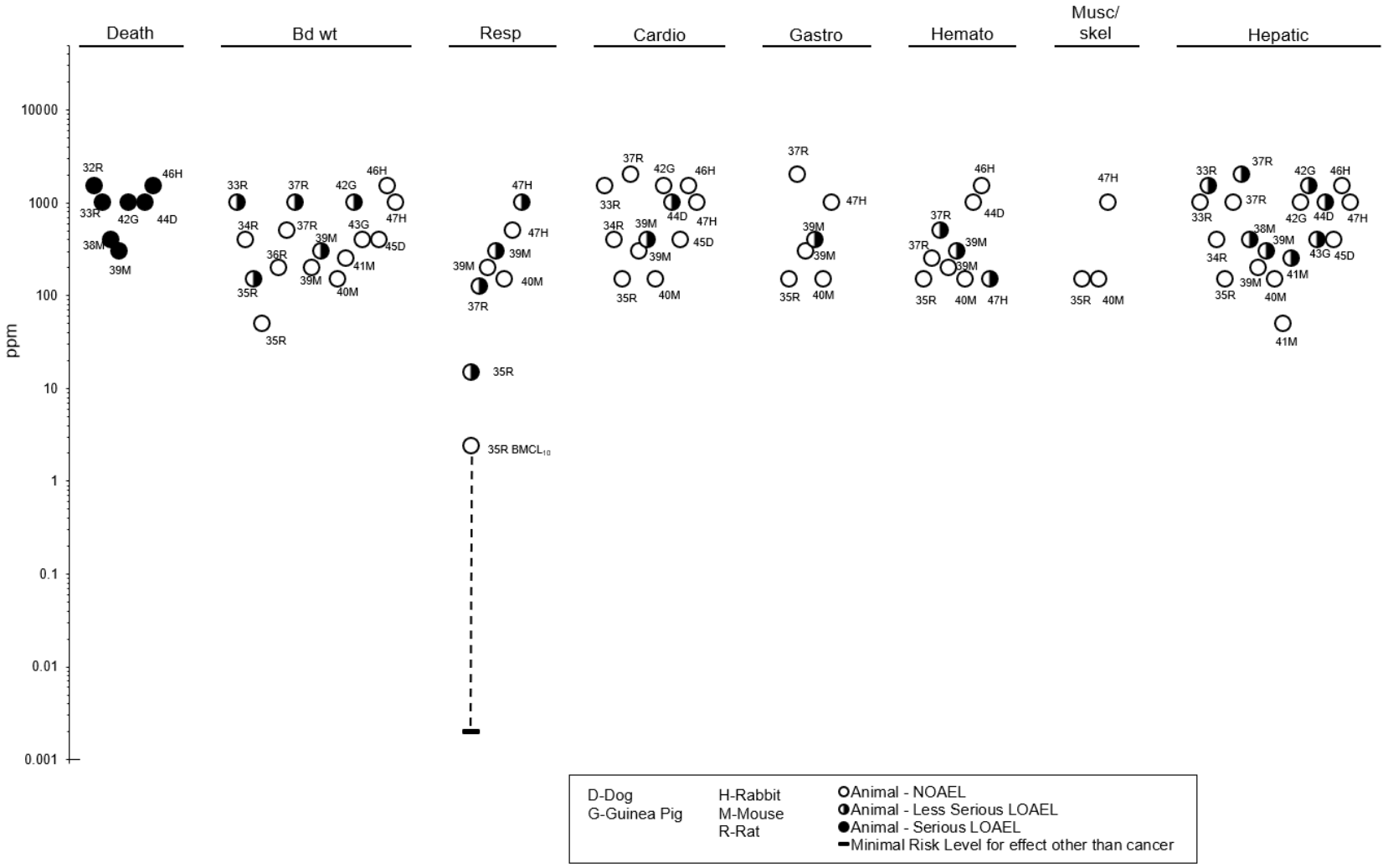


Figure 2-2. Levels of Significant Exposure to 1,2-Dichloropropane – Inhalation
Intermediate (15-364 days)

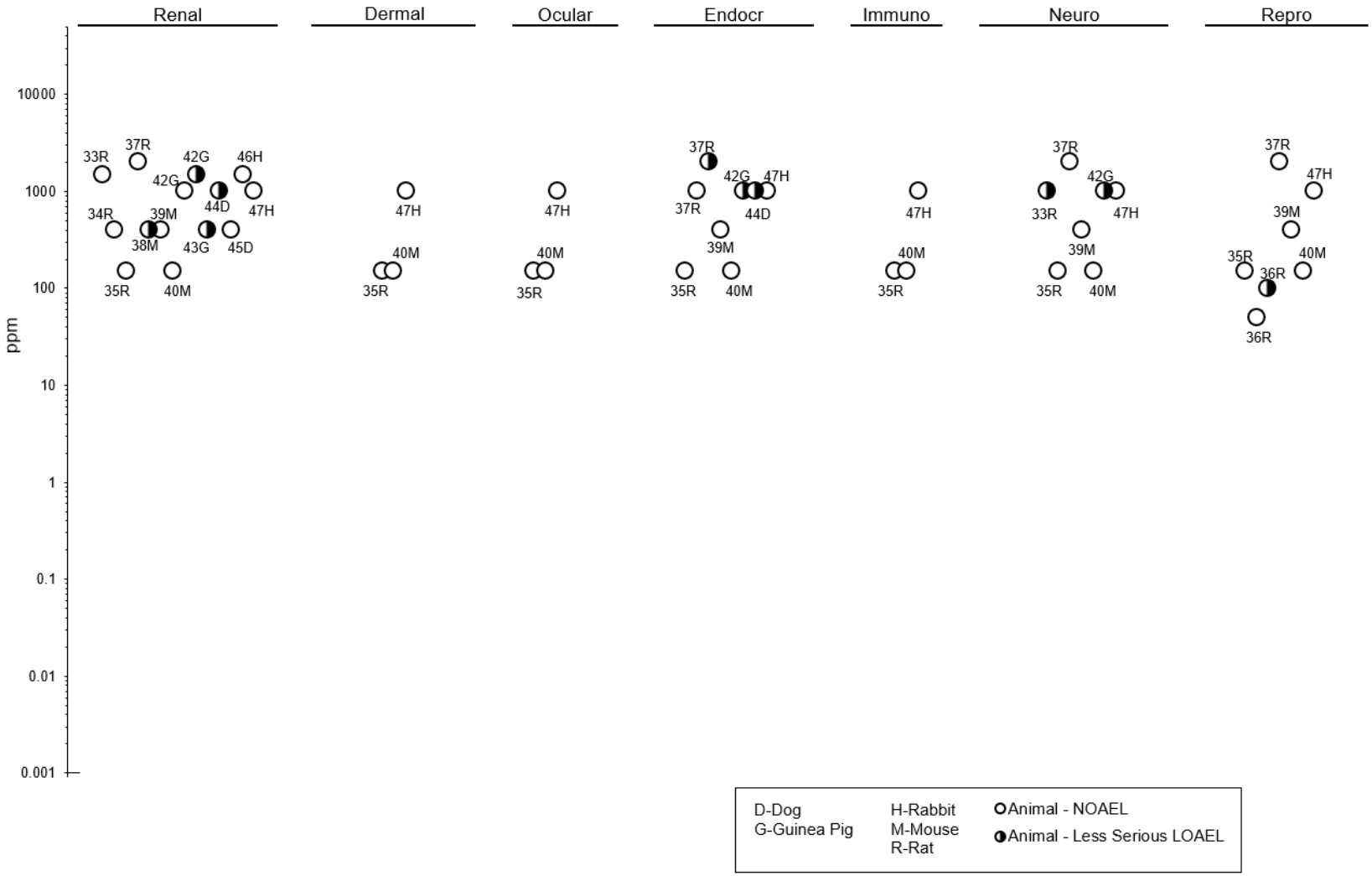


Figure 2-2. Levels of Significant Exposure to 1,2-Dichloropropane – Inhalation
Chronic (≥365 days)

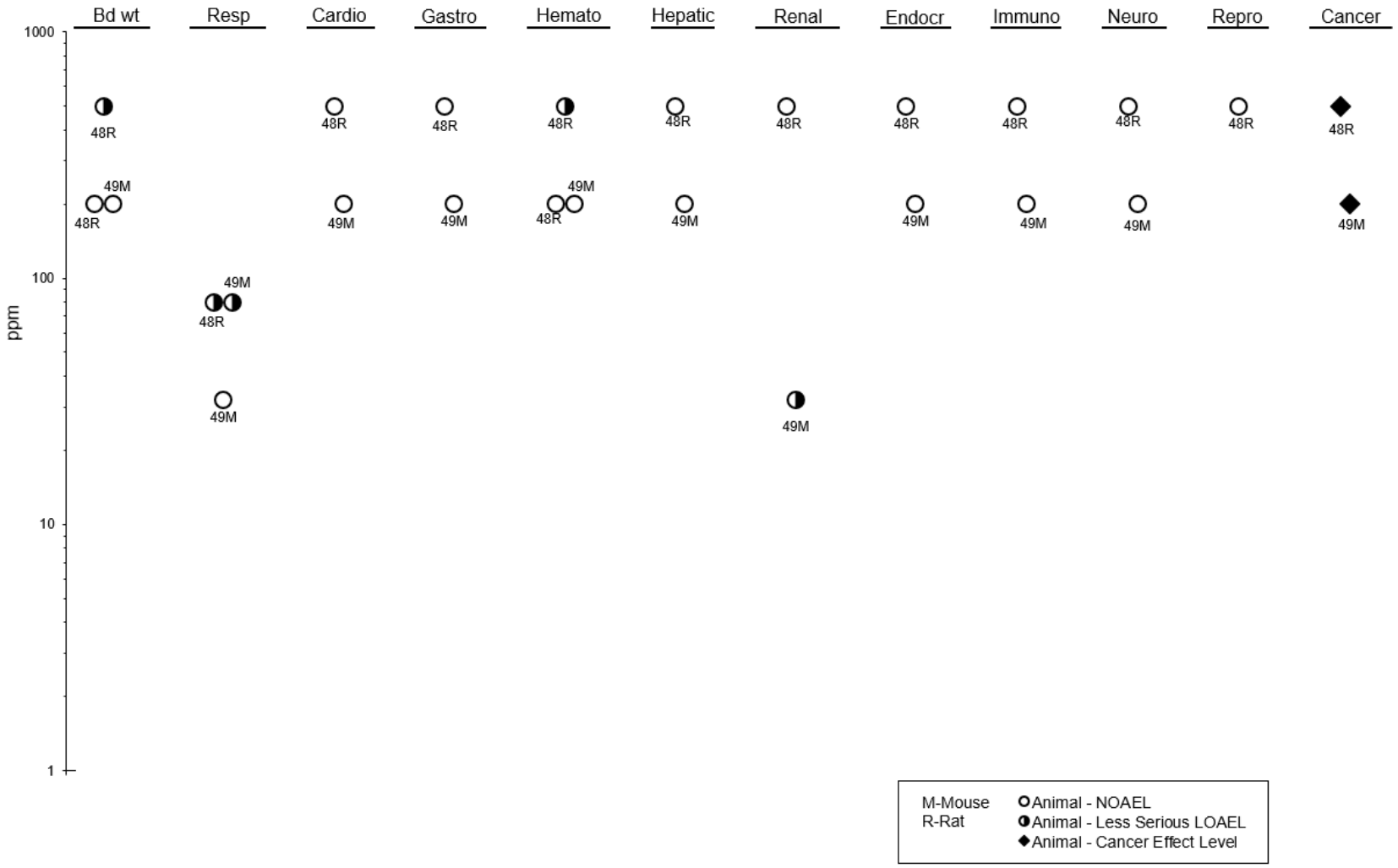


Table 2-2. Levels of Significant Exposure to 1,2-Dichloropropane – Oral

Figure key[a]	Species (strain) No./group	Exposure scenario	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) 6–8 M	1, 5, or 10 days (GO)	0, 100, 250, 500, 750, 1,000	BW, OW, HE, HP, BC, CS, UR	Bd wt	100	250		Decreased body weight gain
					Resp	1,000			
					Gastro	1,000			
					Hemato	100	250	500	Hemolytic anemia at ≥250 mg/kg/day; severe anemia at 500 mg/kg/day
					Hepatic	100	250		Centrilobular necrosis, inflammatory cell infiltration, early proliferation of fibroblasts
					Renal	500	1,000		Increased BUN
					Endocr	1,000			
					Neuro		100	250	Slight CNS depression at ≥100 mg/kg/day; pronounced CNS depression at ≥250 mg/kg/day
Bruckner et al. 1989									
2	Rat (NS) 5 M, 5 F	Once (G)	1,000, 1,470, 2,150, 3,160, 4,680, 6,810, 10,000	BW, CS, GN, LE	Death			1,600	LD_{50}
					Neuro		1,000		CNS depression
Exxon 1981a									
3	Rat (Fischer-344) 10 M, 10 F	14 days (GO)	0, 300, 500	BW, OW, GN, HP, CS, HE, NX	Bd wt	500 F	300 M		>10% decrease in body weight in males
					Hemato	500			
					Hepatic		300		Increased liver weight, degeneration and necrosis of individual hepatocytes, prominent nuclei in centrilobular hepatocytes
					Renal	500			

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

Figure key[a]	Species (strain) No./group	Exposure scenario	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Neuro		300		Transient clinical signs of CNS depression, decreased motor activity
Gorzinski and Johnson 1989									
4	Ray (Wistar) 5–12 M	Once (GO)	2,000	BC, BI, HE	Hemato		2,000		Transient hemolysis
Imberti et al. 1990									
5	Rat (NS) NS	Once (NS)	NS	LE	Death			1,900	LD_{50}
Kennedy and Graepel 1991									
6	Rat (Sprague-Dawley) 30 F	10 days GDs 6–15 (GO)	0, 10, 30, 125	BW, OW, WI, GN, CS, NX	Bd wt	30	125		>10% decrease in maternal body weight gain
					Neuro	30	125		Maternal CNS depression
					Repro	125			No change in the number of corpora lutea, implantations, resorptions, or fetuses
					Develop	30	125		Delayed skull ossification
Kirk et al. 1995									
7	Rat (Sprague-Dawley) 10 F	10 days (GO) GDs 6–15	0, 50, 125, 250, 500	BW, CS, GN, HE, LE, OW, RX	Bd wt	250	500		13% decrease in maternal body weight
					Hemato	500			
					Neuro	125	250	500	Transient CNS depression at ≥250 mg/kg/day; persistent CNS depression at 500 mg/kg/day
					Repro	500			No change in the number of corpora lutea, implantations, resorptions, or fetuses
Kirk et al. 1989									

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

Figure key[a]	Species (strain) No./group	Exposure scenario	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
8	Rat (Fischer-344) 5 M, 5 F	14 days (GO)	0, 125, 250, 500, 1,000, 2,000	BW, GN, CS	Death			2,000	100% mortality
					Bd wt	250 M 500 F	500 M 1,000 F		>10% decrease in body weight
NTP 1986									
9	Rat (Wistar) 6 M, 6 F	Once (G)	145, 230, 366, 582, 926, 1,472	CS, BW, LE	Death			582	6/6 males died at ≥582 mg/kg/day; 2/6, 5/6, and 6/6 females died at 582, 9,266, and 1,472 mg/kg/day, respectively (LD_{50}=487 mg/kg/day)
					Neuro		145	582	Slight CNS depression at all doses; severe CNS depression at ≥582 mg/kg/day
Shell Oil Co. 1982									
10	Rat (NS) 5 M	Once (G)	1,965–2,428	LE	Death			2,000	LD_{50}
Smyth et al. 1969									
11	Mouse (B6C3F1) 5 M	Once (GO)	0, 500	BI, BW, CS, FI, HP, LE, OW, WI	Hepatic		500		Diffuse fatty change
Gi et al. 2015a									
12	Mouse (B6C3F1) 5 M	3 days (GO)	0, 500	BI, BW, CS, FI, HP, LE, OW, WI	Bd wt	500			
					Resp	500			
					Hepatic			500	Extensive centrilobular necrosis and mild fatty change
					Renal	500			
Gi et al. 2015a									
13	Mouse (ddY) NS M	Once (GO)	NS	LE	Death			960	LD_{50}
Matsumoto et al. 1982 [abstract only]									

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

Figure key[a]	Species (strain) No./group	Exposure scenario	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
14	Mouse (B6C3F1) 5 M, 5 F	2 weeks (GO)	0, 125, 250, 500, 1,000, 2,000	BW, GN, CS	Death			500 M 1,000 F	3/5 males died at 500 mg/kg/day, 5/5 males and 4/5 females died at 1,000 mg/kg/day, 100% mortality at 2,000 mg/kg/day
					Bd wt	500			
NTP 1986									
15	Hamster (Golden Syrian) 5 M	Once (GO)	0, 500	BI, BW, CS, FI, HP, LE, OW, WI	Hepatic		500		Mild fatty change
Gi et al. 2015a									
16	Hamster (Golden Syrian) 5 M	3 days (GO)	0, 500→250	BI, BW, CS, FI, HP, LE, OW, WI	Death			500	1/5 dead on day 1 (dose lowered on day 2)
					Bd wt		333		11% decrease in body weight
					Resp	333			
					Hepatic			333	Severe fatty change and extensive centrilobular necrosis
					Renal	333			
Gi et al. 2015a (Dose was decreased from 500 to 250 mg/kg/day on day 2 due to one mortality and toxicity (listlessness) in remaining animals.)									
17	Rabbit (New Zealand) 7 F	13 days (GO) GDs 7–19	0, 25, 100, 250	BW, CS, GN, HE, LE, OW, RX	Death			250	2/7 died
					Hemato	25[b]	100		Maternal anemia. $BMDL_{1SD}$=30 mg/kg/day.
					Repro	100		250	Complete litter resorption (2/5)
Berdasco et al. 1988									

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

Figure key[a]	Species (strain) No./group	Exposure scenario	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
18	Rabbit (New Zealand) 18 F	13 days (GO) GDs 7–19	0, 15, 50, 150	BW, OW, FI, WI, GN, CS, HE	Bd wt	50	150		Decreased body weight gain associated with anorexia
					Hemato	50[b]	150		Maternal anemia. $BMDL_{1SD}$=30 mg/kg/day.
					Repro	150			No change in the number of corpora lutea, implantations, resorptions, or fetuses
					Develop	50	150		Delayed skull ossification
Kirk et al. 1995									
INTERMEDIATE EXPOSURE									
19	Rat (Sprague-Dawley) 15 M	13 weeks 5 days/week (GO)	0, 100, 250, 500, 750	BW, HE, HP, BC, BI, UR	Death			500	>50% mortality
					Bd wt	100	250		~10% decrease in body weight
					Resp	500			
					Gastro	500			
					Hemato		100[c]	250	Hemolytic anemia, including increased serum bilirubin levels and hemosiderosis and hyperplasia of erythropoietic elements of the spleen at ≥100 mg/kg/day; pronounced anemia at ≥250 mg/kg/day. $LOAEL_{ADJ}$= 71 mg/kg/day.
					Hepatic	100	250		Increased relative liver weight at ≥250 mg/kg/day; periportal vacuolization and active fibroplasia at 500 mg/kg/day
					Renal	250	500		Increased relative kidney weight
					Endocr	250 M 500 F	500 M		Fatty adrenal cortex at ≥500 mg/kg/day; vacuolization of the adrenal medulla, lipidosis of the adrenal cortex at 750 mg/kg/day

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

Figure key[a]	Species (strain) No./group	Exposure scenario	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Neuro			500	Pronounced CNS depression (CNS effects not reported at lower doses)
					Repro	250	500		Testicular degeneration, altered sperm production
Bruckner et al. 1989									
20	Rat (Fischer-344) 15 M, 15 F	13 weeks (GO) 5 days/week	0, 20, 65, 200	BW, CS, HP, GN, LE, OW, RX	Bd wt	65 M 200 F	200 M		10% decrease in body weight in males
					Neuro	200			No changes in FOB, strength, motor activity, brain size, or nervous tissue histology
Johnson and Gorzinski 1988									
21	Rat (Sprague-Dawley) 30 M, 30 F	13–21 weeks 2 generations (W)	M: 0, 27, 96, 182 F: 0, 41, 137, 274	BW, CS, DX, FI, GN, HE, HP, OP, OW, RX	Bd wt	96	182		Decreased body weight in F0 and F1 adults
					Hemato	137 F 182 M	274 F		Anemia in F0 dams
					Hepatic	96	182		Granularity of the hepatocellular cytoplasm in high-dose male and female F0 and F1 adults
					Renal	274			
					Ocular	274			
					Repro	274			
					Develop	137		274	Decreased F1 neonatal survival, decreased F1 pup weight during lactation
Kirk et al. 1990 [Doses averaged across both generations]									

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

Figure key[a]	Species (strain) No./group	Exposure scenario	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 (Fischer-344) 10 M, 10 F	13 weeks 5 days/week (GO)	0, 60, 125, 250, 500, 1,000	GN, HP, CS, BW	Death			500 M 1,000 F	50% mortality in males at 500 mg/kg/day; 100% mortality in males and females at 1,000 mg/kg/day
					Bd wt	250 M 500 F	500 M 1,000 F		>10% decrease in body weight
					Resp	1,000			
					Cardio	1,000			
					Gastro	1,000			
					Musc/skel	1,000			
					Hepatic	500	1,000		Centrilobular congestion and necrosis, hepatic fatty changes
					Renal	1,000			
					Dermal	1,000			
					Endocr	1,000			
					Immuno	1,000			
					Neuro	1,000			
					Repro	1,000			
NTP 1986									
23	Mouse (B6C3F1) 5 M	4 weeks 5 days/week (GO)	0, 125, 250	BI, BW, CS, FI, HP, LE, OW, WI	Bd wt	250			
					Resp	250			
					Hepatic		125		Increased liver weight and mild fatty change at ≥125 mg/kg/day; increased serum total cholesterol and triglycerides at 250 mg/kg/day
					Renal	250			
Gi et al. 2015a									
24	Mouse (B6C3F1) 10 M,10 F	13 weeks 5 days/week (GO)	0, 30, 60, 125, 250, 500	BW, GN, HP, CS	Bd wt	500			
					Resp	500			
					Cardio	500			
					Gastro	500			

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

Figure key[a]	Species (strain) No./group	Exposure scenario	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Musc/skel	500			
					Hepatic	500			
					Renal	500			
					Dermal	500			
					Endocr	500			
					Immuno	500			
					Neuro	500			
					Repro	500			
NTP 1986									
25	Hamster (Golden Syrian) 5 M	4 weeks 5 days/week (GO)	0, 125, 250	BI, BW, CS, FI, HE, HP, LE, OW, WI	Death			250	3/5 died
					Bd wt	250			
					Resp	250			
					Hemato	250			
					Hepatic		125		Moderate fatty change
					Renal	250			
Gi et al. 2015a									
26	Hamster (Golden Syrian) 24 M	15–17 weeks 5 days/week (GO)	0, 65, 125	BW, FI, HP, OW, WI	Bd wt	125			
					Hepatic	125			
					Cancer				No tumor promotion activity in liver, pancreas, kidney, or lung following initiation with BOP
Gi et al. 2015b									
CHRONIC EXPOSURE									
27	Rat (Fischer-344) 50 M, 50 F	103 weeks 5 days/week (GO)	M: 0, 62, 125 F: 0, 125, 250	BW, GN, CS, HP	Death			250 F	42% decrease in survival rate
					Bd wt	62 M 125 F	125 M 250 F		>10% decrease in body weight
					Resp	250 F			
					Cardio	250 F			
					Gastro	250 F			

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

Figure key[a]	Species (strain) No./group	Exposure scenario	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Hemato	125 B	250 F		Hemosiderosis of the spleen; blood hematological parameters not evaluated
					Musc/skel	250 F			
					Hepatic	125 B	250 F		Clear cell foci, necrosis
					Renal	250 F			
					Dermal	250 F			
					Immuno	250 F			
					Neuro	250 F			
					Repro	125 M 250 F			
					Cancer			250 F	CEL: mammary tumors (mammary gland hyperplasia at 125 mg/kg/day); no exposure-related neoplasms in males
NTP 1986									
28	Mouse (B6C3F1) 50 M, 50 F	103 weeks 5 days/week (GO)	0, 125, 250	BW, GN, CS, HP	Bd wt	250			
					Resp	250			
					Cardio	250			
					Musc/skel	250			
					Hepatic	125 M 250 F	250 M		Hepatocytomegaly and necrosis
					Renal	250			
					Dermal	250			
					Endocr	250			
					Immuno	250			

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

Figure key[a]	Species (strain) No./group	Exposure scenario	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Neuro	250			
					Repro	250			
					Cancer			125	CEL: hepatic tumors at ≥125 and 250 mg/kg/day in females and males, respectively; thyroid follicular cell tumors in females at 250 mg/kg/day

NTP 1986

[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 an acute-duration oral minimal risk level (MRL). Using benchmark dose modeling, a $BMDL_{1SD}$ value of 30 mg/kg/day was calculated for increased reticulocyte counts in maternal rabbits. The MRL is based on the $BMDL_{1SD}$ of 30 divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability), resulting in an MRL of 0.3 mg/kg/day.
[c]Used to derive an intermediate-duration oral MRL. The LOAEL of 100 mg/kg/day was adjusted for continuous exposure and divided by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability), resulting in an MRL of 0.07 mg/kg/day.

Principal studies for the MRLs.

ADJ = adjusted for continuous exposure; B = both sexes; BC = serum (blood) chemistry; Bd Wt or BW = body weight; BI = biochemical changes; BMDL= 95% lower confidence limit on the benchmark dose (subscripts denote benchmark response: exposure level associated with 10% extra risk or 1 SD change in endpoint); BOP = N-nitrosobis(2-oxopropyl)amine; BUN = blood urea nitrogen; Cardio = cardiovascular; CEL = cancer effect level; CNS = central nervous system; CS = clinical signs; Develop = developmental; DX = developmental toxicity; Endocr = endocrine; F = female(s); F0 = parental generation; F1 = first generation; FI = food intake; FOB = functional observation battery; (G) = gavage; Gastro = gastrointestinal; GD = gestational day; GN = gross necropsy; (GO) = gavage in oil; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; LE = lethality; LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male(s); Musc/skel = musculoskeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; NX = neurological function; OF = organ function; OP = ophthalmology; OW = organ weight; Repro = reproductive; Resp = respiratory; RX = reproductive function; SD = standard deviation; UR = urinalysis; (W) = drinking water; WI = water intake

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

Acute (≤ 14 days)

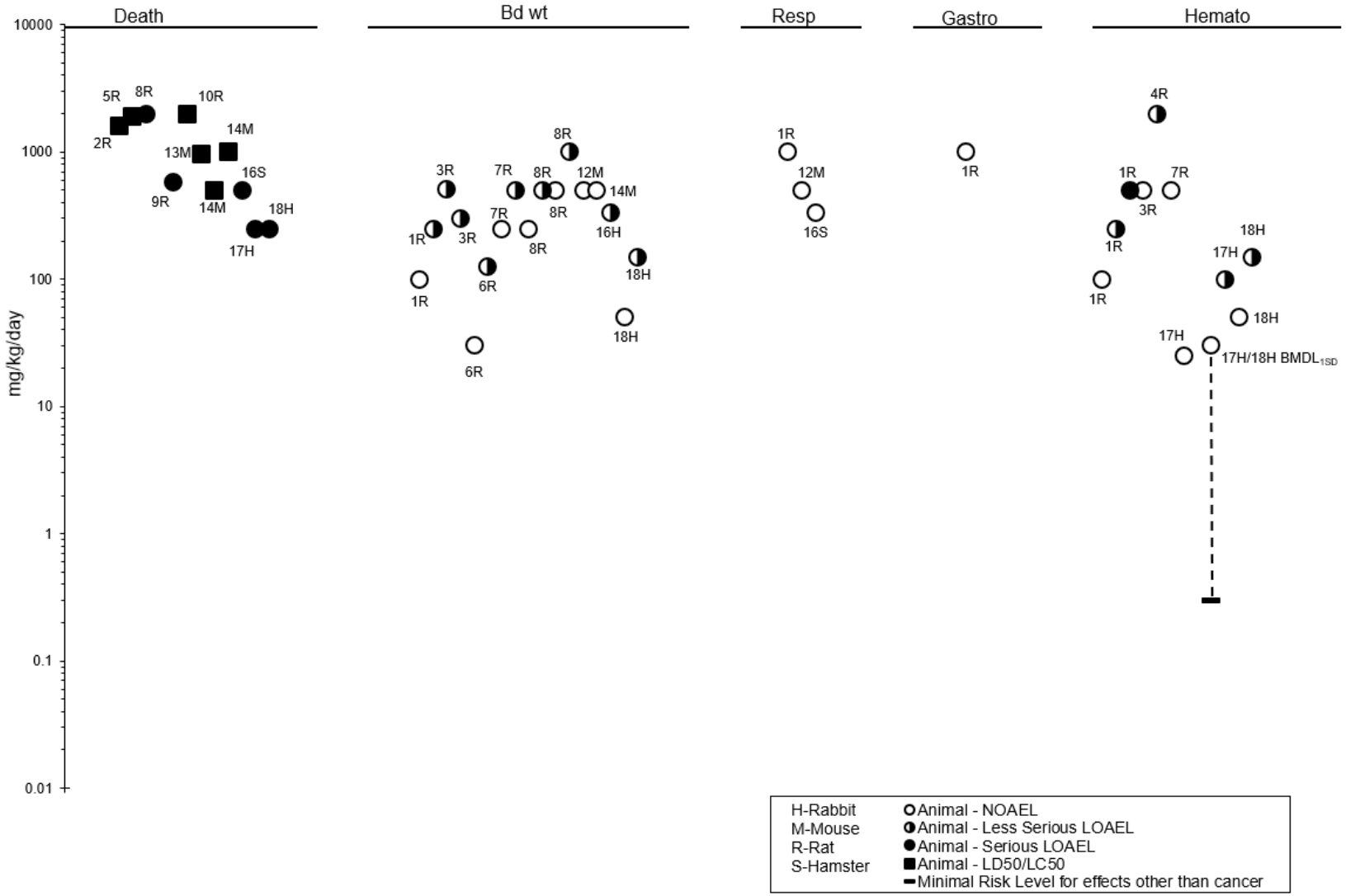


Figure 2-3. Levels of Significant Exposure to 1,2-Dichloropropane – Oral
Acute (≤ 14 days)

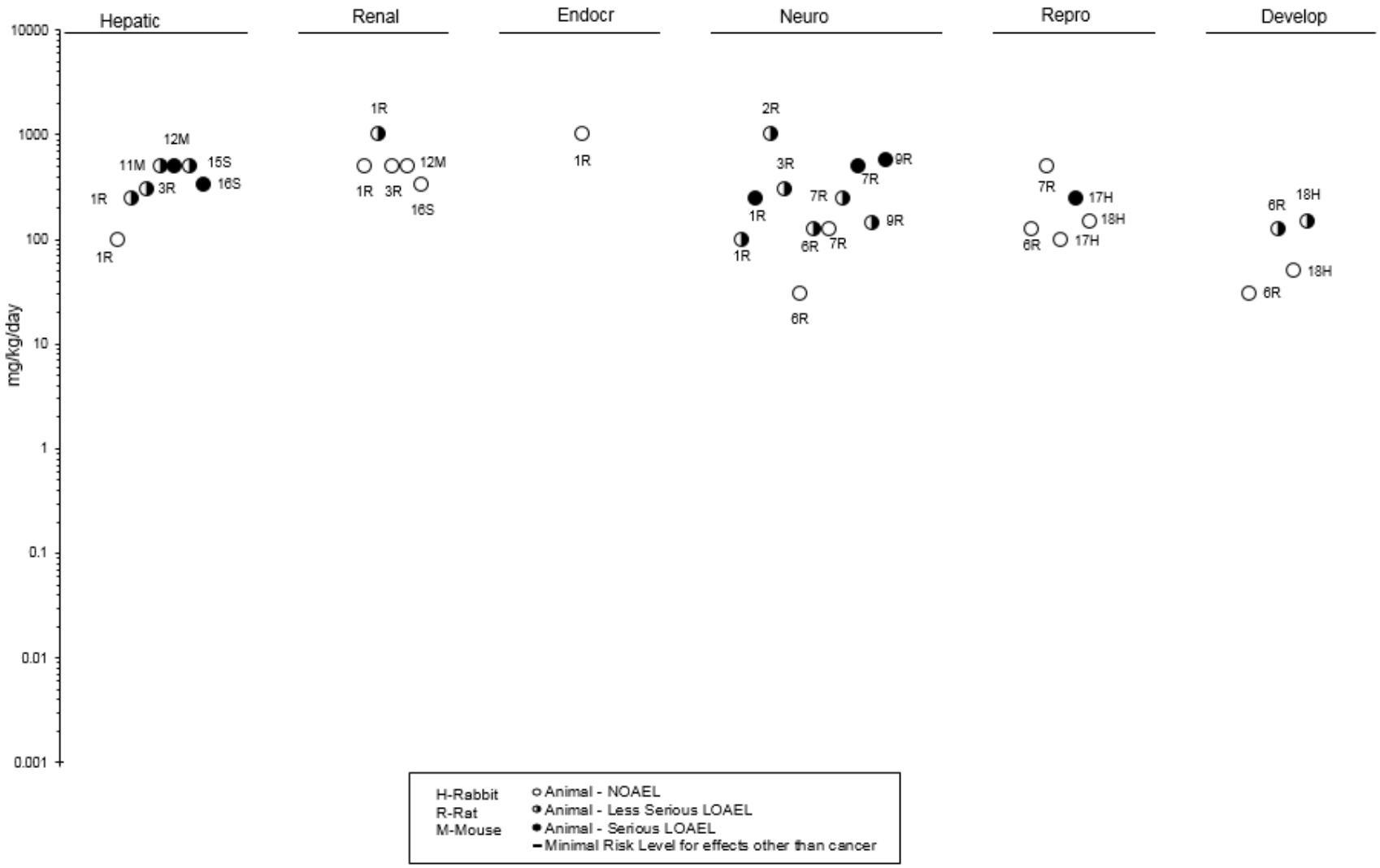


Figure 2-3. Levels of Significant Exposure to 1,2-Dichloropropane – Oral
Intermediate (15-364 days)

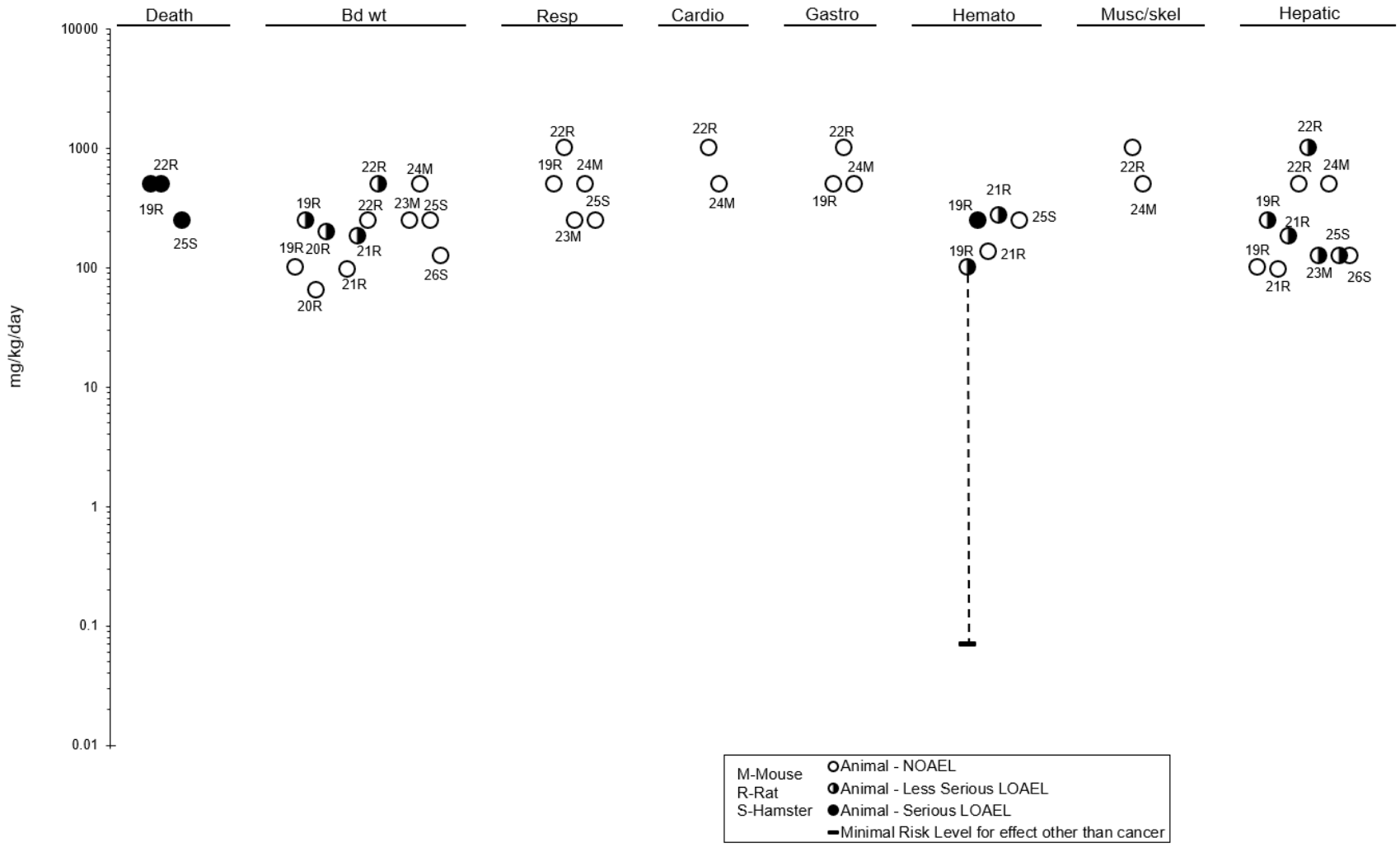


Figure 2-3. Levels of Significant Exposure to 1,2-Dichloropropane – Oral
Intermediate (15-364 days)

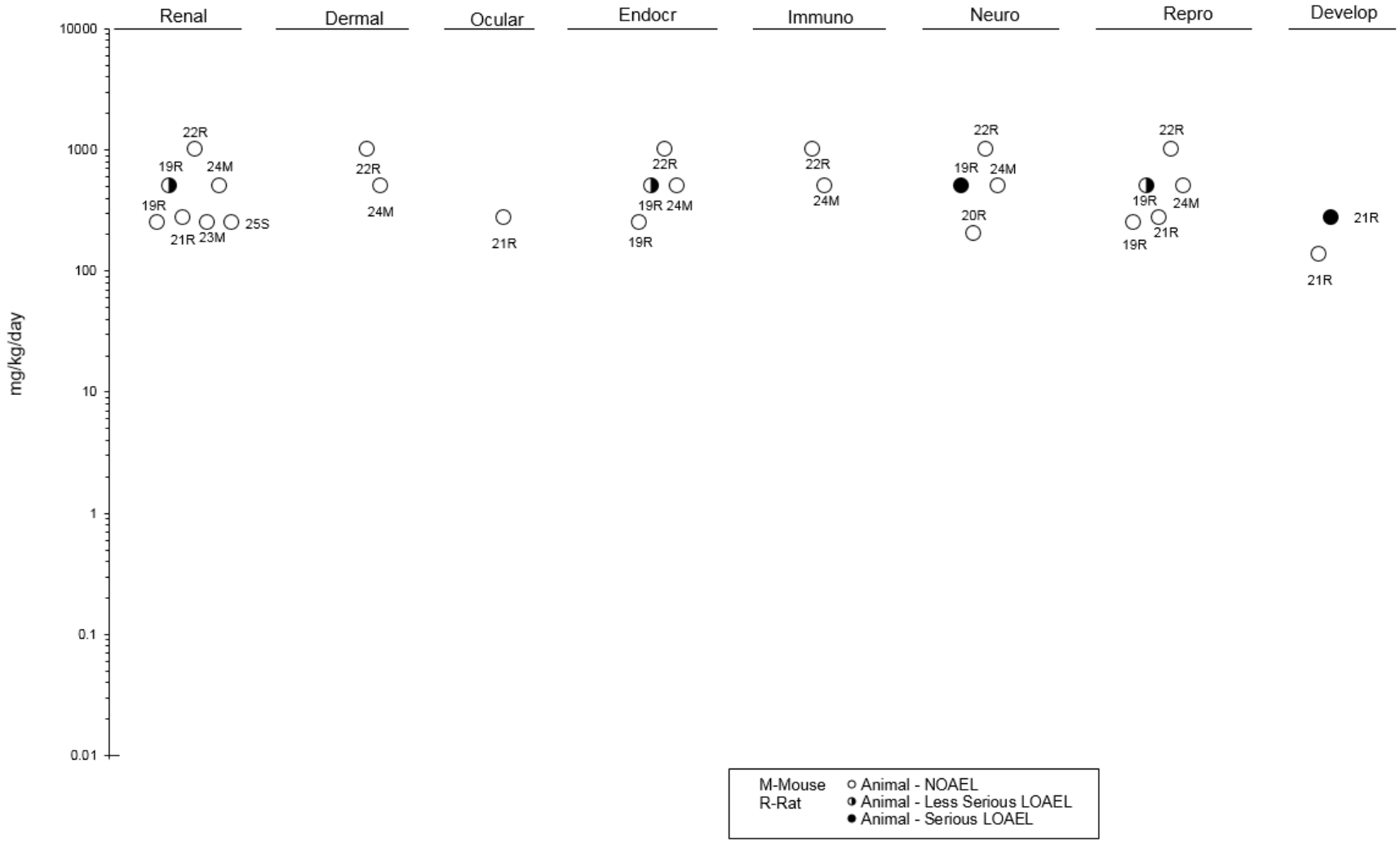


Figure 2-3. Levels of Significant Exposure to 1,2-Dichloropropane – Oral
Chronic (≥365 days)

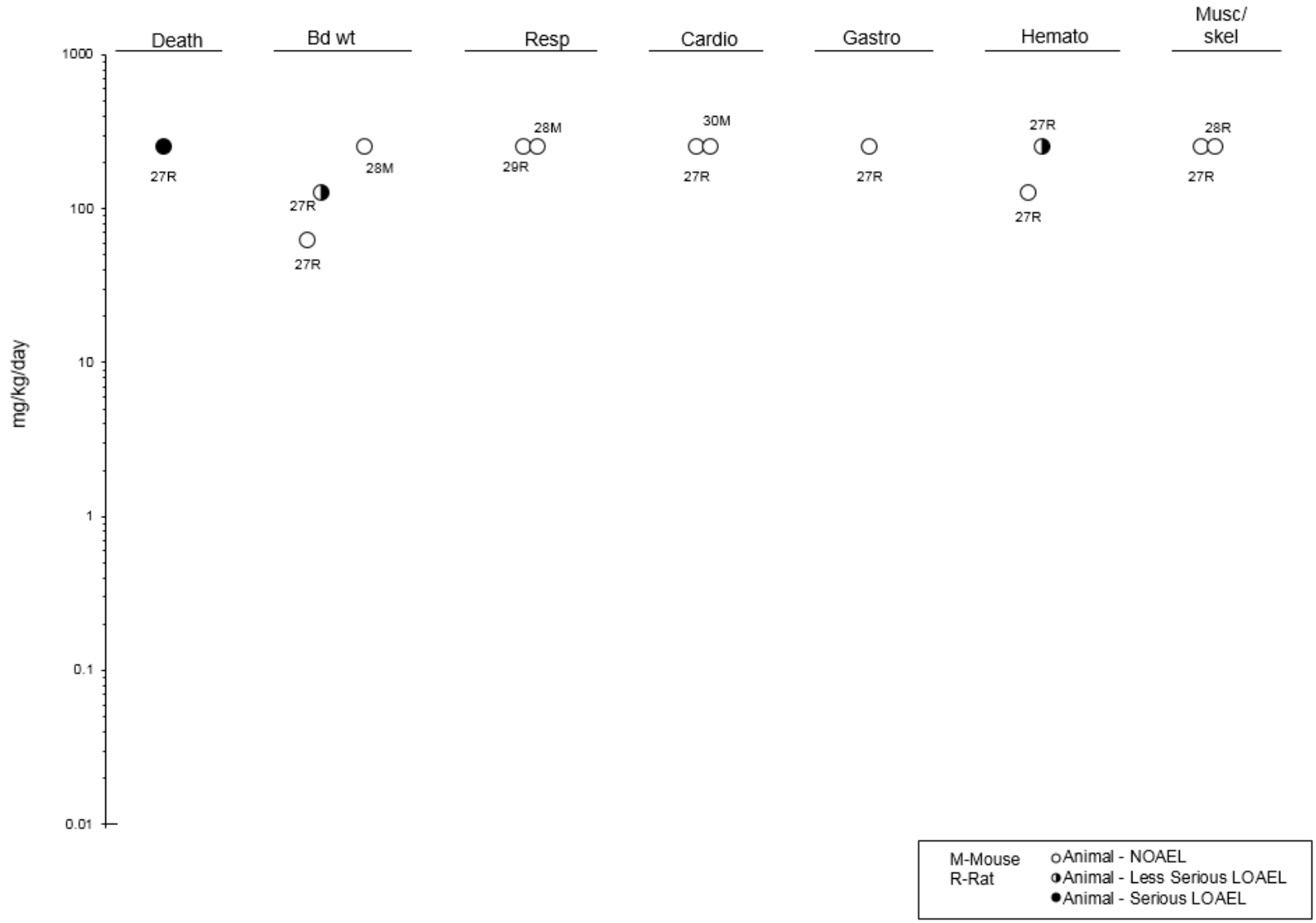


Figure 2-3. Levels of Significant Exposure to 1,2-Dichloropropane – Oral
Chronic (≥365 days)

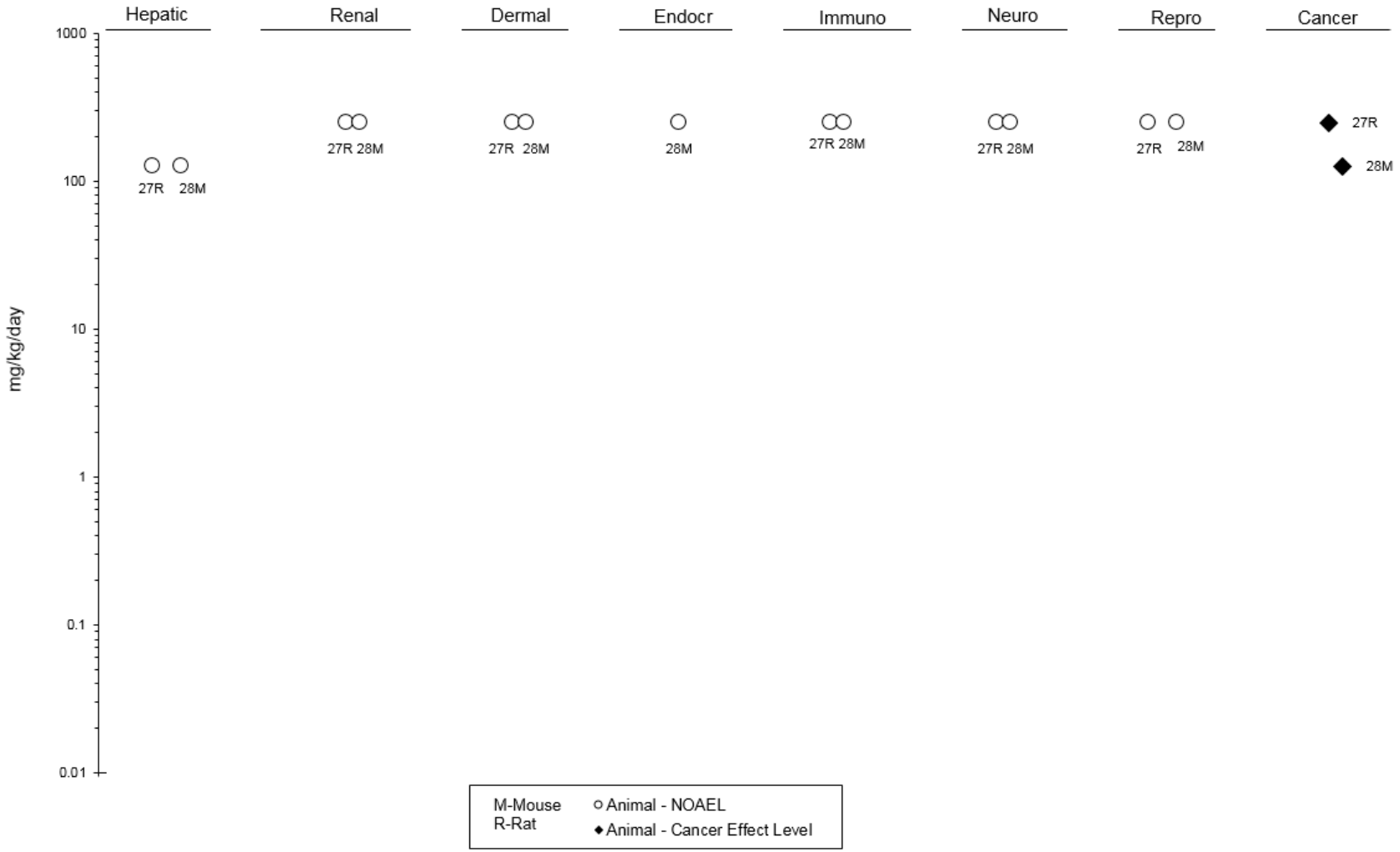


Table 2-3. Levels of Significant Exposure to 1,2-Dichloropropane – Dermal

Species (strain) No./group	Exposure scenario	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE								
Rat (Wistar) 6 M, 6 F	24 hours	2.34 g/kg	BW, CS, LE	Bd wt	2.34 g/kg			
				Dermal		2.34 g/kg		Erythema
Shell Oil Co. 1982								
Mouse (C57Bl/6J) 5 NS	7 days 1 time/day	0, 2.73, 5.75, 8.75 mL/kg	BC, CS, HP	Dermal		2.73 mL/kg		Dermatitis and angiogenesis of the skin
Jin et al. 2019								
Guinea pig (NS) 5–10 M, 5–10 F	NS	0.58 g/mL (induction), 0.29 g/mL (challenge)	CS	Immuno		0.58 g/mL		Skin sensitizer
Shell Oil Co. 1982								
Rabbit (NS) 2 M, 2 F	NS	0, 3.16 g/kg	BW, CS, GN, LE	Bd wt	3.16 g/kg			
				Dermal		3.16 g/kg		Erythema and edema
Exxon 1981b								
Rabbit (New Zealand) 3 M, 3 F	24 hours	1.16 g/mL	CS	Dermal		1.16 g/mL		Skin irritation; chemical burns in females
Shell Oil Co. 1982								
Rabbit (NS) 4 M	24 hours	8.3–9.2 mL/kg	LE	Death			8.75 mL/kg	LD_{50}
Smyth et al. 1969								

Bd Wt or BW = body weight; CS = clinical signs; F = female(s); GN = gross necropsy; Immuno = immunological; LD_{50} = lethal dose, 50% kill; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); NOAEL = no-observed-adverse-effect level; NS = not specified

2.2 DEATH

Worker fatalities have been reported following accidental inhalation overexposure to commercial mixtures containing 1,2-dichloropropane (e.g., from chemical spills) (reviewed by ACGIH 2014; IARC 1986). Fatalities have also been reported in cases of accidental or intentional ingestion or intentional inhalation abuse ("sniffing" or "huffing") of large amounts of mixtures containing 1,2-dichloropropane, such as household stain removers (Di Nucci et al. 1988; Larcan et al. 1977; Pozzi et al. 1985). Following these exposures, death was primarily attributed to cardiac arrest, shock, or liver failure, but cases of renal failure, pulmonary edema, disseminated intravascular coagulation, and severe hemolytic anemia have also been reported. The exposure levels in these case studies cannot be determined accurately; therefore, they are not included in the LSE tables or figures.

Exposure-related deaths have been reported in laboratory animals following acute or intermediate inhalation exposures; acute, intermediate, and chronic oral exposures; and acute dermal exposures.

Inhalation Exposure. Smyth et al. (1969) reported an 8-hour inhalation LC_{50} value of 2,000 ppm in rats. Following a single 4-hour inhalation exposure, the concentration at which the first death was observed in rats (approximate lethal concentration [ALC]) was 2,000 ppm; the study authors assumed that the ALC was half of the 4-hour LC_{50} (Kennedy and Graepel 1991). 1,2-Dichloropropane was reported in a group of chemicals causing death in two, three, or four out of six rats following exposure to 2,000 ppm for 4 hours, but the exact number of deaths was not reported for 1,2-dichloropropane alone (Carpenter et al. 1949). No mortality was observed in rats exposed to concentrations up to 1,060 ppm for 4–6 hours (Di Nucci et al. 1990; Drew et al. 1978; Nitschke and Johnson 1983), but 3/12 rats died following a 7-hour exposure to 1,600 ppm (Heppel et al. 1946a). In acute-duration, repeat-exposure studies (6–8 hours/day, up to 14 exposures), mortality in rats was observed at concentrations as low as 1,600 ppm, but not at concentrations ≤1,000 ppm (Heppel et al. 1946a; Highman and Heppel 1946; Nitschke and Johnson 1983; Zhang et al. 2015).

In an intermediate-duration study, exposure-related mortality was observed in rats exposed to 1,500 ppm for 15 days (7 hours/day), but not 1,000 ppm, when a standard diet was used (Heppel et al. 1946b, 1946b). However, 100% mortality was observed after 3–4 exposures to 1,000 or 1,500 ppm when rats were fed a low-casein, high-fat diet; the study authors suggested that this may be due to decreased detoxification due to deficiency of sulfur-containing amino acids associated with this diet (Heppel et al. 1946b). In another series of intermediate-duration studies in Wistar and Sprague-Dawley rats,

8/18 Wistar rats died following exposure to 1,500 ppm (7 hours/day, up to 35 exposures) and 9/27 Wistar rats and 16/18 Sprague-Dawley rats died following exposure to 1,000 ppm (7 hours/day, up to 97 exposures) (Heppel et al. 1946a). However, in other studies, no exposure-related deaths were observed in rats following intermittent exposure to concentrations up to 2,000 ppm for up to 13 weeks (Nitschke et al. 1988; Sekiguchi et al. 2002; Umeda et al. 2010), or 80–500 ppm for 2 years (Umeda et al. 2010).

In mice, a 10-hour inhalation LC_{50} value of 480 ppm was reported; all mice (22–26 animals) died after a single exposure of 4 hours to 1,000 or 1,500 ppm, while 3/10 mice died after a single 2-hour exposure to 1,500 ppm (Dow Chemical Co. 1968). Heppel et al. (1946b) reported 100% mortality in mice following a single 7-hour exposure to ≥1,000 ppm. Similarly, 100% mortality was observed in mice within 24 hours of a 6-hour exposure to 1,500 ppm; at 500 ppm mice became lethargic and 2/5 mice died within 3 days of exposure (Nitschke and Johnson 1983). Zhang et al. (2015) also reported 100% mortality in mice exposed to ≥1,000 ppm for 8 hours/day for up to 7 days or ≥400 ppm for 6 hours/day for up to 14 days. Heppel et al. (1948) reported 44% mortality after a single 7-hour exposure to 400 ppm, with 96% mortality following 37 exposures to 400 ppm (4–7 hours/exposure). No compound-related mortality was observed in mice exposed to concentrations up to 300 ppm for 6 hours/day, 4–5 days/week (Nitschke and Johnson 1983), or up to 250 ppm for 4 weeks (8 hours/day) (Zhang et al. 2018). In longer-duration studies, exposure-related deaths were observed at ≥300 ppm following intermittent exposure for 13 weeks (6 hours/day, 5 days/week), but not at concentrations ≤200 ppm for up to 2 years (Matsumoto et al. 2013; Nitschke et al. 1988).

In guinea pigs, 7/20 animals died after two or three 7-hour exposures to 2,200 ppm (Highman and Heppel 1946). Heppel et al. (1946b) also reported deaths in 11/16 guinea pigs exposed to 2,200 ppm for 7 hours/day for up to 5 days; no deaths occurred with exposure to 1,600 ppm. In another study, 100% mortality was observed in guinea pigs exposed to ≥3,000 ppm for 8 hours/day for up to 7 days; no mortality was observed at concentrations ≤1,000 ppm (Zhang et al. 2015). Intermediate-duration exposure resulted in 3/12 deaths after exposure to 1,000 ppm (7 hours/day) for up to 39 exposures and 5/18 deaths after exposure to 1,500 ppm (7 hours/day) for up to 126 exposures (Heppel et al. 1946a).

In hamsters, 100% mortality was observed following exposure to concentrations ≥1,000 ppm for 8 hours/day for up to 7 days or ≥800 ppm for 6 hours/day for up to 14 days (Zhang et al. 2015).

In rabbits, no compound-related mortality was observed following intermittent exposure to concentrations up to 1,000 ppm for up to 18 weeks (6–7 hours/day, 5 days/week) (Heppel et al. 1946a; Nitschke and Johnson 1983; Nitschke et al. 1988). Exposure to 2,200 ppm for 7 hours/day for up to 8 days resulted in 2/4 deaths in exposed rabbits, and exposure to 1,500 ppm for 7 hours/day for up to 39 days resulted in 1/4 deaths (Heppel et al. 1946a).

One study reported death in 4/5 dogs and 1/4 puppies exposed to 1,2-dichloropropane for up to 128 days (7 hours/day) at 1,000 ppm; however, severe anorexia was also observed and starvation was the likely cause of death (Heppel et al. 1946a).

Oral Exposure. An acute study in Wistar rats statistically determined an oral LD_{50} value of 487 mg/kg (Shell Oil Co. 1982). However, other reported oral LD_{50} values in rats of unspecified strain(s) are much higher, ranging from 1,600 to 2,000 mg/kg (Exxon 1981a; Kennedy and Graepel 1991; Smyth et al. 1969). Since the strain was not reported in the studies with the higher LD_{50} values, it is unclear if the discrepancy is due to strain susceptibility. However, Imberti et al. (1990) did not report any deaths in Wistar rats following a single exposure to 2,000 mg/kg. In acute-duration, repeat-exposure studies up to 14 days, 100% mortality was observed at 2,000 mg/kg/day in F344 rats (NTP 1986), with no exposure-related deaths in F344 or Sprague-Dawley rats at doses up to 1,000 mg/kg/day (Bruckner et al. 1989; Gorzinski and Johnson 1989; Kirk et al. 1989, 1995). In intermediate-duration studies, exposure-related mortalities were reported in both F344 and Sprague-Dawley rats following exposure to ≥500 mg/kg/day for 13 weeks, but not ≤250 mg/kg/day for 13–21 weeks (Bruckner et al. 1989; Johnson and Gorzinski 1988; Kirk et al. 1990; NTP 1986). In chronic studies, increased mortality was observed in F344 female rats following exposure to 250 mg/kg/day for up to 103 weeks (NTP 1986).

An oral LD_{50} value of 960 mg/kg was reported in ddY mice in an abstract by Matsumoto et al. (1982). No deaths were reported in B6C3F1 mice exposed once to 500 mg/kg (Gi et al. 2015a). In acute-duration, repeat-exposure studies up to 14 days, mortality occurred in B6C3F1 mice at ≥500 mg/kg/day (Gi et al. 2015a; NTP 1986). No mortalities clearly related to exposure were observed following intermediate-duration exposure to doses up to 500 mg/kg/day (Gi et al. 2015a; NTP 1986) or chronic-duration exposure to doses up to 250 mg/kg/day for 103 weeks (NTP 1986).

In rabbits, death occurred in 1/2, 2/2, and 2/2 animals exposed to 250, 500, and 1,000 mg/kg/day for 13 days (Kirk et al. 1988); however, this study was not included in the LSE table due to inadequate animal number. In pregnant rabbits, 2/7 does died following exposure to 250 mg/kg/day on gestation

days (GDs) 6–15; however, it is unclear if the deaths were exposure-related because the cause of death was undetermined (Berdasco et al. 1988). No exposure-related mortalities were observed in pregnant rabbits exposed to doses up to 150 mg/kg/day (Berdasco et al. 1988; Kirk et al. 1995).

In hamsters, no deaths occurred after a single exposure to 500 mg/kg; however, 3-day exposure at that dose caused death in 1/5 animals (Gi et al. 2015a). In a 4-week study, 1/5 and 3/5 animals died at 125 and 250 mg/kg/day, respectively (Gi et al. 2015a). No exposure-related deaths were observed in hamsters exposed to doses up to 125 mg/kg/day for 15–17 weeks (Gi et al. 2015b).

Dermal Exposure. A dermal LD_{50} of 8.75 mL/kg (10.2 g/kg) was calculated for rabbits (Smyth et al. 1969). The treatment site was covered with an impervious plastic film for 24 hours following application and the animals were observed for 14 days. No rats or rabbits died following a single dermal application of 2.34–3.16 g/kg (Exxon 1981b; Shell Oil Co. 1982).

2.3 BODY WEIGHT

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

Decreased body weight following exposure to 1,2-dichloropropane has been reported in laboratory animals following acute-, intermediate-, and chronic-duration inhalation exposures and acute, intermediate, and chronic oral exposures.

Inhalation Exposure. Body weight loss was reported in rats and guinea pigs following acute exposure to ≥1,600 ppm (7 hours/day) for 5–8 days (Heppel et al. 1946a). Nitschke and Johnson (1983) also reported decreased body weight gain in rats at ≥100 ppm during a 2-week exposure (6 hours/day, 4–5 days/week), but this finding was attributed to decreased food intake. No body weight effects were reported in mice or rabbits following acute exposure to concentrations up to 300 and 1,000 ppm, respectively (Nitschke and Johnson 1983; Wang et al. 2019).

In intermediate-duration studies, the lowest LOAEL for decreases in body weight >10% was in F344 male rats exposed to 150 ppm for 13 weeks (6 hours/day, 5 days/week); the associated NOAEL was 50 ppm (Nitschke et al. 1988). No body weight effects were observed in similarly exposed female F344 rats exposed at concentrations up to 150 ppm (Nitschke et al. 1988). However, another study using the

same exposure protocol in F344/DuCrj rats reported a NOAEL and LOAEL of 500 and 1,000 ppm, respectively, for both male and female rats (Umeda et al. 2010). Body weights were also unaffected in female rats exposed to concentrations up to 200 ppm for 8 hours/day for 21–24 days (Sekiguchi et al. 2002). Decreased body weight gains were observed in rats and guinea pigs exposed to ≥1,000 ppm for >30 days (7 hours/day; lowest concentration evaluated), but not similarly exposed rabbits at concentrations up to 1,500 ppm (Heppel et al. 1946a). In mice, terminal body weights were decreased by >10% in males exposed at ≥300 ppm for 13 weeks (6 hours/day, 5 days/week), but not at lower concentrations; body weights were comparable to controls in females up to 400 ppm (Matsumoto et al. 2013; Nitschke et al. 1988). Body weight in male mice was not affected at concentrations up to 250 ppm for 4 weeks (8 hours/day, 7 days/week) (Zhang et al. 2018). No body weight effects were observed in rabbits similarly exposed to concentrations up to 1,000 ppm (Nitschke et al. 1988).

In chronic-duration studies, terminal body weights in rats were significantly decreased by 11% in males and 8% in females exposed to 500 ppm for up to 104 weeks (6 hours/day, 5 days/week); body weights were comparable to controls in rats and mice at concentrations up to 200 ppm (Matsumoto et al. 2013; Umeda et al. 2010).

Oral Exposure. Body weight decreases >10% were observed in F344 male rats at ≥500 mg/kg/day and female rats at ≥1,000 mg/kg/day following gavage exposure for 2 weeks (5 days/week) (NTP 1986). In F344 rats exposed via gavage 7 days/week for 2 weeks, male rats showed body weight decreases >10% at ≥300 mg/kg/day; no body weight effects were noted in female rats at doses up to 500 mg/kg/day (Gorzinski and Johnson 1989). In Sprague-Dawley rats, a significant dose-related decrease in body weight gain was observed in males, following exposure to doses ≥250 mg/kg/day via gavage for 10 days (Bruckner et al. 1989). No body weight effects were observed in mice exposed to 500 mg/kg/day for 3 days or at doses up to 2,000 mg/kg/day for 2 weeks (5 days/week) (Gi et al. 2015a; NTP 1986). In hamsters, an 11% decrease in body weight was observed in animals exposed to 500 mg/kg/day for 1 day followed by 250 mg/kg/day for 2 days (time-weighted average [TWA] of 333 mg/kg/day); the initial dose was decreased after one animal died and the surviving animals showed listlessness (Gi et al. 2015a).

In intermediate- and chronic-duration studies, decreased body weight was observed in Sprague-Dawley rats at ≥250 mg/kg/day for 13 weeks (Bruckner et al. 1989); in F344 male and female rats at doses as low as 200 and 1,000 mg/kg/day, respectively, for 13 weeks (Johnson and Gorzinski 1988; NTP 1986); and in F344 male and female rats at 125 and 250 mg/kg/day, respectively, for up to 103 weeks (NTP 1986). No body weight effects were observed in B6C3F1 mice exposed to doses up 250 mg/kg/day for 4 weeks,

500 mg/kg/day for 13 weeks, or 250 mg/kg/day for up to 103 weeks (Gi et al. 2015a; NTP 1986). No body weight effects were observed in hamsters exposed to doses up 250 mg/kg/day for 4 weeks (Gi et al. 2015a)

In a 2-generation study in rats, both F0 and F1 parental animals showed decreased body weight following exposure to drinking water concentrations up to 0.24% (estimated doses of 152–293 mg/kg/day per sex per generation), but not concentrations ≤0.10% (estimated doses of 83–148 mg/kg/day per sex per generation) (Kirk et al. 1990). Similarly, maternal body weight gain was significantly decreased in rat dams and rabbit does exposed to 125 mg/kg/day on GDs 6–15 or 7–19, respectively, but not ≤30 mg/kg/day (Kirk et al. 1995). In dose-range finding studies with fewer animals, significant maternal body weight effects were not observed in rats or rabbits at doses up to 250 mg/kg/day, but rat dams showed significant weight loss at 500 mg/kg/day (Berdasco et al. 1988; Kirk et al. 1989).

Dermal Exposure. No changes in body weight were observed in rats or rabbits following a 24-hour dermal exposure to 2.34 or 3.16 g/kg, respectively, of undiluted 1,2-dichloropropane (Shell Oil Co. 1982).

2.4 RESPIRATORY

Rubin (1988) described respiratory effects in humans resulting from exposure to an accidental spill of 2,000 gallons of 1,2-dichloropropane. The exposure resulted in chest discomfort, dyspnea, and cough in some of the patients, indicating that 1,2-dichloropropane is a respiratory tract irritant. Following a railway accident in which 3,000 gallons of a mixture containing 4 parts *o*-dichlorobenzene, 2 parts 1,2-dichloropropane, and 1 part ethylene dichloride spilled, 10 workers died and 3 additional men were hospitalized with pulmonary edema, emphysema, bronchopneumonia, tachycardia, and destruction of the airways (see ACGIH 2014). Air concentrations of 1,2-dichloropropane were not measured or estimated in either spill.

Nasal lesions have been observed in rats, mice, and rabbits following acute-, intermediate-, and chronic-duration inhalation exposure to 1,2-dichloropropane; the rat appears to be the most sensitive species. Evidence of nasal tumors in rats and lung tumors in mice following chronic inhalation exposure to 1,2-dichloropropane is discussed in Section 2.19 (Cancer). No respiratory lesions have been observed in rats, mice, or hamsters orally exposed to 1,2-dichloropropane; however, the nasal cavity has not been evaluated in any available oral exposure studies.

Inhalation Exposure. Nasal cavity lesions were observed in rats, mice, and rabbits following acute exposure to 1,2-dichloropropane for 2 weeks (6 hours/day, 4–5 days/week) (Nitschke and Johnson 1983). Degeneration of the nasal mucosa was found in all rats exposed to concentrations ≥100 ppm (lowest concentration tested); the severity of the lesions increased in a concentration-related manner. Additional effects observed in rats at ≥300 ppm included inflammatory and exudative changes in the nasal tissue. Degeneration of the nasal mucosa was also found in all mice exposed to 300 ppm, although lesions were less severe than those observed in rats. At 100 ppm, nasal lesions were only observed in 2/5 female mice and 0/5 male mice; no lesions were observed at 30 ppm. In the rabbits, some animals showed slight nasal mucosa degeneration at 1,000 ppm, with no exposure-related nasal lesions at ≤300 ppm. Therefore, rats appear to be the most sensitive species to the respiratory effects of 1,2-dichloropropane exposure.

Nasal cavity lesions were also reported in rats, mice, and rabbits following intermittent exposure for 13 weeks (6 hours/day, 5 days/week). Nasal cavity lesions were observed in rats exposed to ≥15 ppm, including hyperplasia of the respiratory epithelium at ≥15 ppm, degeneration of the olfactory epithelium at ≥50 ppm, atrophy of the olfactory epithelium at ≥125 ppm, submucosal inflammation at ≥150 ppm, and inflammation of the respiratory epithelium at ≥1,000 ppm (Nitschke et al. 1988; Umeda et al. 2010). No NOAEL was established for nasal lesions in rats. In mice, nasal lesions, including respiratory metaplasia, atrophy, necrosis, and desquamation, were observed following exposure to ≥300 ppm, but not at concentrations up to 200 ppm (Matsumoto et al. 2013; Nitschke et al. 1988). Rabbits exposed to 1,000 ppm also had slight degeneration of the olfactory epithelium; no adverse effects on the respiratory system were found in rabbits exposed to concentrations up to 500 ppm (Nitschke et al. 1988).

Nasal lesions were reported in rodents following chronic-duration exposure to 1,2-dichloropropane for up to 104 weeks (6 hours/day, 5 days/week). In rats, nasal cavity lesions were observed at ≥80 ppm (lowest concentration tested), including atrophy of olfactory epithelium, inflammation of the respiratory epithelium, squamous cell metaplasia of respiratory epithelium, and hyperplasia of the transitional epithelium at ≥80 ppm and squamous cell hyperplasia and hyperplasia of the submucosal glands at ≥200 ppm (Umeda et al. 2010). In mice, nasal lesions were also observed at ≥80 ppm, but not at 32 ppm (Matsumoto et al. 2013). Observed lesions in mice included atrophy of olfactory epithelium at ≥80 ppm and metaplasia of the olfactory epithelium and submucosal glands at 200 ppm.

Lung congestion was observed in rats and guinea pigs following acute exposure to 1,2-dichloropropane at 2,200 ppm (1–8 days, 7 hours/day; only concentration evaluated) (Heppel et al. 1946a). However, increased incidences of nonneoplastic histopathological lung lesions were not observed following

1,2-dichloropropane exposure in rats, mice, or rabbits following exposure to concentrations up to 2,000 ppm for 13 weeks (Matsumoto et al. 2013; Nitschke et al. 1988; Umeda et al. 2010) or rats or mice following exposure to concentrations up to 500 ppm for 104 weeks (Matsumoto et al. 2013; Umeda et al. 2010)

Oral Exposure. No histopathologic changes in the lungs were observed following acute (Bruckner et al. 1989; Gi et al. 2015a), intermediate (Bruckner et al. 1989; Gi et al. 2015a; NTP 1986), or chronic (NTP 1986) oral exposure in rats, mice, or hamsters. The highest NOAEL values for each duration category are 1,000, 1,000, and 250 mg/kg/day, respectively. The nasal cavity has not been assessed in any available oral exposure study.

Mechanisms of Respiratory Tract Toxicity. There are no specific mechanisms of toxicity proposed for respiratory tract toxicity. However, available data indicate that glutathione depletion may underlie toxicity in the liver and kidney as well as hemolytic anemia (Di Nucci et al. 1988; Imberti et al. 1990). This mechanism may be applicable to respiratory tract toxicity as well, as it has been proposed for other chemicals known to lead to glutathione depletion (e.g., naphthalene; ATSDR 2005). However, this mechanism has not been specifically evaluated for respiratory tract toxicity associated with 1,2-dichloropropane exposure. The only available data are from an *in vitro* study that showed that 1,2-dichloropropane caused decreased cell viability in cultured human embryonic lung fibroblasts (Kawasaki et al. 2015).

2.5 CARDIOVASCULAR

Cardiovascular collapse and cardiac arrest have been reported in fatal cases of 1,2-dichloropropane poisoning (Di Nucci et al. 1988; Larcan et al. 1977; see also ACGIH 2014). These effects are likely secondary to CNS depression and widespread systemic toxicity, as opposed to direct effects on the cardiovascular system. Tachycardia was reported in a 43-year-old man following prolonged dermal exposure (~5 hours) to a commercial fixative (30–40% 1,2-dichloropropane, 33–38% toluene); the increased heart rate was attributed to hyperkalemia secondary to acute renal failure (Fiaccadori et al. 2003). No additional information regarding the potential for cardiovascular effects in humans following exposure to 1,2-dichloropropane was available.

No histopathological changes were observed in the heart or aorta following acute- or intermediate-duration exposure to concentrations up to 2,200 ppm (6–7 hours/day, 5 days/week) in rats, guinea pigs,

rabbits, or dogs (Heppel et al. 1946a, 1948; Nitschke et al. 1988; Umeda et al. 2010) or chronic-duration exposure in rats to concentrations up to 500 ppm for up to 104 weeks (Umeda et al. 2010). A "ground glass" appearance was noted in mice exposed to 400 ppm for 6 hours/day, 5 days/week, for 13 weeks, which was an exposure level associated with significant mortality (Matsumoto et al. 2013). No exposure-related changes in the heart or aorta of mice were observed at concentrations ≤300 ppm for 13 weeks (Matsumoto et al. 2013; Nitschke et al. 1988), or ≤200 ppm for up to 104 weeks (Matsumoto et al. 2013).

No adverse effects of 1,2-dichloropropane on the cardiovascular system were found following histological examination of the heart in rats following gavage doses up to 1,000 mg/kg/day for 13 weeks, or 125 mg/kg/day in males and 250 mg/kg/day in females for 103 weeks (5 days/week) (NTP 1986). Similarly, no histopathological changes were observed in mice following gavage doses up to 500 mg/kg/day for 13 weeks, or 250 mg/kg/day for 103 weeks (5 days/week) (NTP 1986).

2.6 GASTROINTESTINAL

Pozzi et al. (1985) reported vomiting and abdominal pain in a young woman who admitted to intentional inhalation abuse of a stain remover ("sniffing" or "huffing") to alleviate nervousness the previous night. The stain remover consisted of primarily (98%) of 1,2-dichloropropane, but an exposure estimate was not reported. In another case report, abdominal pain and vomiting upon hospitalization were observed in a 73-year-old woman who fell asleep in close proximity to an open bottle of stain remover containing 1,2-dichloropropane (Lucantoni et al. 1992). The woman was admitted to the hospital 3 days after exposure. Nausea was reported in a 43-year-old man following prolonged dermal exposure (~5 hours) to a commercial fixative (30–40% 1,2-dichloropropane, 33–38% toluene); he was admitted to the hospital for renal failure 4 days after exposure (Fiaccadori et al. 2003). Vomiting was also reported in a case of accidental ingestion of a commercial preparation of 1,2-dichloropropane (trilene) (Chiappino and Secchi 1968). All cases showed complete recovery.

No histopathological changes in the gastrointestinal system were observed in rats intermittently exposed (6 hours/day, 5 days/week) to air concentrations of 1,2-dichloropropane up to 2,000 ppm for 13 weeks (Nitschke et al. 1988; Umeda et al. 2010), or up to 500 ppm for up to 104 weeks (Umeda et al. 2010). Forestomach hyperplasia was noted in mice exposed to 400 ppm for 6 hours/day, 5 days/week, for 13 weeks, which was an exposure level associated with significant mortality (Matsumoto et al. 2013). No histopathological changes in the gastrointestinal system were observed in mice at concentrations up to 300 ppm for 13 weeks (Matsumoto et al. 2013; Nitschke et al. 1988), or up to 200 ppm for up to

104 weeks (Matsumoto et al. 2013). In rabbits, no histopathological changes in the gastrointestinal system were observed at concentrations up to 1,000 ppm, 6 hours/day, 5 days/week for 13 weeks (Nitschke et al. 1988).

No histopathological changes in the gastrointestinal system were observed in rats exposed to gavage doses up to 1,000 mg/kg/day for 1–10 days (Bruckner et al. 1989) or 13 weeks (5 days/week) (Bruckner et al. 1989; NTP 1986). Similarly, gastrointestinal lesions were not observed in mice exposed to gavage doses up to 500 mg/kg/day for 13 weeks (5 days/week) (NTP 1986). However, erosion of the mucosal lining of the stomach was observed in 2/2 rabbits exposed to gavage doses of 500 or 1,000 mg/kg/day for 13 days; no erosion was observed at 250 mg/kg/day (Kirk et al. 1988). The rabbit study was not included in the LSE tables or figures due to inadequate animal number.

Rats that were treated with 1,2-dichloropropane doses as high as 250 mg/kg/day (5 days/week) for 103 weeks did not have histological alterations in the gastrointestinal tract (NTP 1986). In female mice that were treated by gavage with 1,2-dichloropropane doses of 125 or 250 mg/kg/day (5 days/week) for 103 weeks, acanthosis of the forestomach was observed in 5/50 and 4/50 of animals, respectively. In male mice similarly treated, this effect was only observed in 2/50 animals from the high-dose group. Because it is uncertain whether the acanthosis is compound-related due to low incidences and lack of increase in incidence with increasing dose, a LOAEL or NOAEL for gastrointestinal effects following chronic oral exposure to 1,2-dichloropropane cannot be determined for mice.

2.7 HEMATOLOGICAL

Hemolytic anemia, disseminated intravascular coagulation, and/or severe blood coagulation disorders have been reported in several accidental or intentional cases of 1,2-dichloropropane poisoning via ingestion (Di Nucci et al. 1988; Perbellini et al. 1985) or inhalation exposure (Lucantoni et al. 1991, 1992; Pozzi et al. 1985). Some of these cases were fatal. Disseminated intravascular coagulation was also reported in a 43-year-old man 4 days after a prolonged dermal exposure (~5 hours) to a commercial fixative containing 30–40% 1,2-dichloropropane and 33–38% toluene; the patient made a full recovery (Fiaccadori et al. 2003). Exposure levels could not be accurately determined in these cases, so a LOAEL could not be determined. No hematological changes were observed in 11 Japanese print shop workers diagnosed with CCA following exposure to 1,2-dichloropropane and/or dichloromethane (see Table 2-4 in Section 2.19 Cancer for more details); air levels were not measured, but estimated exposure levels

based on reported quantities were 190–310 ppm 1,2-dichloropropane and 140–360 ppm dichloromethane (Kumagai et al. 2013, 2014).

As observed in human case reports, hemolytic anemia has been observed in rats, mice, and rabbits following exposure to high levels of 1,2-dichloropropane.

Inhalation Exposure. No exposure-related changes were observed in the hematological parameters in rats or mice exposed to concentration up to 1,000 ppm and 300 ppm, respectively, for 2 weeks (6 hours/day, 4–5 days/week) (Nitschke and Johnson 1983).

Hemolytic anemia, characterized by increased serum bilirubin levels, bone marrow congestion, hemosiderosis in the spleen, and increased hematopoiesis in the spleen and bone marrow, was observed following exposure for 13 weeks (6 hours/day, 5 days/week) in rats at ≥500 ppm, mice at ≥300 ppm, and rabbits at ≥150 ppm; no hematological effects were observed in rats or mice similarly exposed to concentrations up to 250 ppm for up to 104 weeks (Matsumoto et al. 2013; Nitschke et al. 1988; Umeda et al. 2010). However, exposure to 500 ppm for 6 hours/day, 5 days/week for 104 weeks only caused mild anemia in female, but not male, rats, with no exposure-related changes in hematopoietic tissues in either sex (Umeda et al. 2010). The discrepancies in findings between the intermediate- and chronic-duration studies in rats at 500 ppm were not discussed or explained by the study authors.

In older studies, splenic hemosiderosis was observed in acute studies in rats, guinea pigs, and rabbits exposed to ≥1,600 ppm and in intermediate-duration studies in rats exposed to ≥1,000 ppm and dogs exposed to 400 ppm, but hematological parameters were not assessed in these studies (Heppel et al. 1946a, 1948). In rabbits and dogs, no clear evidence of hematological changes was observed following intermediate-duration exposure to concentrations up to 1,500 ppm (Heppel et al. 1946a). These studies are considered inadequate due to poor study design (e.g., low animal number), lack of comprehensive endpoint evaluation, and/or poor data reporting, and are not included in the LSE tables or figures.

Oral Exposure. Transient hemolysis was reported in Wistar rats exposed once to a gavage dose of 2,000 mg/kg/day (Imberti et al. 1990); however, no exposure-related changes in hematological parameters were observed in Sprague-Dawley rats exposed once to a gavage dose up to 2,000 mg/kg/day (Bruckner et al. 1989). In repeated-dose, acute-duration rat studies, a dose-related increase in the severity of hemolytic anemia was found in male Sprague-Dawley rats treated with gavage doses ≥250 mg/kg/day for 5 or 10 consecutive days, or ≥100 mg/kg/day for 13 weeks (5 days/week) (Bruckner et al. 1989). As

observed in inhalation studies, findings were characterized by increased serum bilirubin levels, hemosiderosis, and hyperplasia of erythropoietic elements of the hematopoietic tissues. Evidence of anemia was also observed in F0 rat dams exposed to gavage doses of 254 mg/kg/day for up to 21 weeks in a 2-generation study (Kirk et al. 1990), and rabbit does exposed to gavage doses ≥100 mg/kg/day on GDs 7–19 (Berdasco et al. 1988; Kirk et al. 1995). However, no exposure-related hematological changes were observed in male or female F344 rats exposed to gavage doses up to 500 mg/kg/day for 14 days (Gorzinski and Johnson 1989), or Sprague-Dawley rat dams exposed to gavage doses up 500 mg/kg/day on GDs 6–15 (Kirk et al. 1989).

No exposure-related hematological changes or lesions in hematopoietic tissues were observed in hamsters exposed to gavage doses up to 250 mg/kg/day for 4 weeks (Gi et al. 2015a). Gi et al. (2015a) also reported a lack of compound-related histopathological lesions in the hematopoietic tissues of B6C3F1 mice or Golden Syrian hamsters exposed to gavage doses of 500 mg/kg/day for 3 days or to doses of 250 mg/kg/day for 4 weeks (5 days/week); however, blood hematology was not evaluated in these studies. Similarly, no compound-related histopathological lesions in hematopoietic tissues were observed in F344/N rats and B6C3F1 mice treated 5 days/week with 1,2-dichloropropane at doses of 30–1,000 mg/kg/day for 13 weeks, or 62–125 mg/kg/day for 103 weeks (NTP 1986). However, female rats exposed to 250 mg/kg/day for 103 weeks showed evidence of slight hemosiderosis of the spleen in 20/47 animals, compared with 0/50 controls (NTP 1986). NOAELs from these studies are not included in the LSE or Figure 2-3 due to lack of clinical hematological parameter evaluation.

Mechanisms of Hemolytic Anemia. Imberti et al. (1990) proposed that glutathione depletion may contribute to hematological toxicity because a statistically significant association between GSH depletion in the blood and hemolysis was observed following acute oral exposure to 1,2-dichloropropane. When the glutathione precursor, N-acetylcysteine, was administered prior to 1,2-dichloropropane, hemolysis did not occur. Glutathione depletion is a well-established mechanism of hemolytic anemia following exposure to naphthalene (ATSDR 2005). Based on intraperitoneal injection experiments, Trevisan et al. (1989) proposed that with repeated exposure, adaptive mechanisms in the liver may compensate for glutathione depletion. This may explain the apparent decrease in susceptibility to hemolytic anemia in laboratory animals with increasing duration of exposure to 1,2-dichloropropane (see Inhalation Exposure section above).

2.8 MUSCULOSKELETAL

Rhabdomyolysis was reported in a 43-year-old man 4 days after a prolonged dermal exposure (~5 hours) to a commercial fixative containing 30–40% 1,2-dichloropropane and 33–38% toluene; the patient made a full recovery (Fiaccadori et al. 2003). No additional studies were located regarding musculoskeletal effects in humans following exposure to 1,2-dichloropropane.

No adverse effects of 1,2-dichloropropane on the musculoskeletal system were found following histological examination of the bone of rats and mice exposed to air concentrations of 1,2-dichloropropane up to 150 ppm, or rabbits exposed to concentrations up to 1,000 ppm, 6 hours/day, 5 days/week for 13 weeks (Nitschke et al. 1988). Similarly, no adverse effects of 1,2-dichloropropane on the musculoskeletal system were found following histological examination of the sternum or costochondral joints of rats and mice exposed 5 days/week via gavage to 1,2-dichlropropane doses as high as 1,000 mg/kg/day for 13 weeks, or 250 mg/kg/day for 103 weeks (NTP 1986).

2.9 HEPATIC

Based on several case reports of occupational exposure, accidental or intentional ingestion, or intentional inhalation abuse (“sniffing” or “huffing”) of large amounts of mixtures containing 1,2-dichloropropane, the liver is one of the main target organs for the toxic effects of 1,2-dichloropropane (Chiappino and Secchi 1968; Di Nucci et al. 1988; Larcan et al. 1977; Lucantoni et al. 1991, 1992; Kubo et al. 2015; Perbellini et al. 1985; Pozzi et al. 1985; Secchi and Alessio 1968; Thorel et al. 1986). Effects associated with exposure include altered serum liver enzymes, impaired liver function, toxic hepatitis, centrilobular and midlobular hepatic necrosis, and liver failure. Recovery was complete in nonfatal cases. Impaired liver function, jaundice, and acute hepatocellular necrosis were also reported in a 43-year-old man 4 days after a prolonged dermal exposure (~5 hours) to a commercial fixative containing 30–40% 1,2-dichloropropane and 33–38% toluene; the patient made a full recovery within 2 weeks (Fiaccadori et al. 2003). Exact exposure levels cannot be determined in these case studies, so a LOAEL cannot be determined.

Several case-series reports and retrospective cohort studies of Japanese print shop workers suggest a potential association between 1,2-dichloropropane (and other chlorinated solvents) and CCA, a rare form of bile duct cancer (Kubo et al. 2014a, 2014b; Kumagai et al. 2013, 2014, 2016; Sobue et al. 2015; Yamada et al. 2014, 2015a, 2015b); see Table 2-4 in Section 2.19 (Cancer) for more details. Elevated serum γ-glutamyl transferase (GGT), alanine aminotransferase (ALT), and aspartate aminotransferase

(AST) levels and jaundice were reported in exposed individuals with CCA (Kubo et al. 2014b; Kumagai et al. 2014).

Hepatic damage has been consistently observed following inhalation and oral exposure to 1,2-dichloropropane in multiple species. Evidence of hepatic tumors following chronic exposure to 1,2-dichloropropane is discussed in Section 2.19 (Cancer).

Inhalation Exposure. In rats, fat-like droplets were observed following intermittent exposure to 3,000 ppm for 7 days (8 hours/day); no exposure-related lesions were observed at ≤1,000 ppm (Zhang et al. 2015). Consistent with these findings, Nitschke and Johnson (1983) found no exposure-related histopathological lesions in the liver of rats exposed to concentrations up to 1,500 ppm for 6 hours. However, exposure to 1,000 ppm for 2 weeks (6 hours/day, 4–5 days/week) resulted in mild liver hepatocellular hypertrophy and elevated liver weights in rats (Nitschke and Johnson 1983). In other acute rat studies, no alterations in serum levels of liver enzymes, which would indicate liver damage, were observed in rats exposed to concentrations up to 1,060 ppm for 4 hours (Di Nucci et al. 1990; Drew et al. 1978); however, highest concentrations were not identified as NOAELs due to lack of liver weight and histology evaluations. Hepatic lesions were observed at lower concentrations in mice and hamsters. In mice, observations included extensive hemorrhagic necrosis after exposure to 500 ppm for 6 hours, vacuolization after exposure to ≥300 ppm for 7 days (8 hours/day) or ≥200 ppm for 14 days (6 hours/day), and increased liver weight and hepatocellular hypertrophy after exposure to 300 ppm for 2 weeks (6 hours/day, 4–5 days/week) (Nitschke and Johnson 1983; Zhang et al. 2015). Increased relative liver weights, altered clinical chemistry (increased AST and ALT), and hepatocellular hypertrophy, necrosis, and granular degeneration were also observed in mice exposed to 300 ppm for 6 hours; these changes were not observed in mice exposed for up to 4 hours (Wang et al. 2019). However, no changes in liver weight or clinical chemistry were observed in mice exposed to concentrations up to 400 ppm for 2 days (6 hours on day 1, 3 hours on day 2) (Toyooka et al. 2017). In hamsters, a slight dilation of hepatic sinusoids was observed following exposure to 400 ppm for 14 days (6 hours/day), but not at concentrations up to 300 ppm for 7–14 days (6–8 hours/day) (Zhang et al. 2015). No exposure-related hepatic lesions were observed at concentrations up to 1,000 ppm in guinea pigs (7 days, 8 hours/day) (Zhang et al. 2015), or rabbits (2 weeks, 6 hours/day, 4–5 days/week) (Nitschke and Johnson 1983).

Increased absolute and relative liver weights were observed in female rats exposed to concentrations ≥500 ppm for 13 weeks (6 hours/day, 5 days/week); however, histopathological changes were only observed at 2,000 ppm (in both sexes) (Umeda et al. 2010). No exposure-related hepatic changes were

observed in male or female rats similarly exposed to concentrations up 250 ppm for 13 weeks (Nitschke et al. 1988), or to 500 ppm for 104 weeks (Umeda et al. 2010). In mice, increased absolute liver weight, changes in clinical chemistry (increased ALT and bilirubin), focal necrosis, and bile duct hyperplasia were seen in males exposed to 250 ppm for 4 weeks (8 hours/day, 7 days/week) (Zhang et al. 2018). Following exposure for 13 weeks (6 hours/day, 5 days/week), increased absolute and relative liver weights accompanied by swelling of centrilobular hepatocytes was observed after exposure to concentrations ≥300 ppm; clinical chemistry alterations (increased AST, ALT, and alkaline phosphatase [ALP] in males), fatty and vacuolic changes, mineralization, and necrosis were also observed at 400 ppm (Matsumoto et al. 2013). No exposure-related hepatic changes were observed in male or female mice similarly exposed to concentrations up to 200 ppm for 13 or 104 weeks (Matsumoto et al. 2013; Nitschke et al. 1988).

Evidence from older studies support that hepatic damage (fatty degeneration, centrilobular congestion, necrosis) can occur following acute exposure to 2,200 ppm in rats and guinea pigs, ≥1,600 ppm in rabbits, and ≥400 ppm in mice (Heppel et al. 1946a, 1948; Highman and Heppel 1946). Similar effects were noted in intermediate-duration studies in rats at ≥1,500 ppm, guinea pigs and mice at ≥400 ppm, and dogs at 1,000 ppm; no adverse effects were observed in the livers of rabbits at concentrations up to 1,500 ppm (Heppel et al. 1946a, 1948; Highman and Heppel 1946).

Oral Exposure. Hepatic effects were consistently observed in laboratory animals acutely exposed to 1,2-dichloropropane at doses as low as 250 mg/kg/day. Liver necrosis, characterized by degenerative effects on the centrilobular hepatocytes and mild to moderate hepatitis, was observed in Sprague-Dawley rats exposed to gavage doses ≥250 mg/kg/day for 1, 5, or 10 consecutive days (Bruckner et al. 1989). No adverse hepatic effects were observed at 100 mg/kg/day. Consistent with these findings, increased liver weight, hepatocyte degeneration and necrosis, and prominent nuclei in centrilobular hepatocytes were observed in F344 rats exposed to gavage doses ≥300 mg/kg/day for 14 days (Gorzinski and Johnson 1989), and hepatic necrosis was observed in rabbits exposed to ≥500 mg/kg/day for 13 days (Kirk et al. 1988). However, the rabbit study (Kirk et al. 1988) was considered inadequate due to low animal numbers per group (n=2). In mice and hamsters, mild and diffuse fatty changes were observed following single gavage administration of 500 mg/kg (only dose tested) (Gi et al. 2015a). The severity of fatty changes increased and extensive centrilobular necrosis was observed when mice received the same dose for 3 days, and when hamsters received 500 mg/kg for 1 day followed by 250 mg/kg/day for 2 days (TWA: 333 mg/kg/day) (Gi et al. 2015a). The dose in hamsters was decreased on day 2 due to one death and toxicity (listlessness) in remaining animals.

Other acute studies evaluated limited hepatic endpoints, but they were not included in the LSE tables or figures due to lack of histological examinations. Increased serum ALT and AST were reported in rats exposed once to 2,000 mg mg/kg/day via gavage (only dose level) (Imberti et al. 1990); liver weights and histology were not assessed in these studies. No changes were observed in rat liver weight following a single exposure to 55 mg/kg (Di Nucci et al. 1988). No changes in maternal liver weight were observed in pregnant rats exposed to gavage doses up to 500 mg/kg/day on GDs 6–15, or pregnant rabbits exposed to gavage doses up to 250 mg/kg/day on GDs 7–19 (Berdasco et al. 1988; Kirk et al. 1989, 1995); serum chemistry and histology were not assessed.

Hepatic lesions were observed at doses as low as 125 mg/kg/day following intermediate exposure to 1,2-dichloropropane; however, observed lesions and NOAEL and LOAEL values were not consistent between all studies. Periportal vacuolization and fibroplasia were found in Sprague-Dawley rats treated with ≥500 mg/kg/day for 13 weeks (5 days/week), with increased liver weights at ≥250 mg/kg/day (Bruckner et al. 1989). No adverse hepatic effects were observed at 100 mg/kg/day. In a 2-generation study with Sprague-Dawley rats, granularity of the hepatocellular cytoplasm was observed in F0 and F1 adults following exposure to estimated doses of 152–293 mg/kg/day in drinking water doses for 13–21 weeks; however, the adversity of this effect, accompanied by increased liver weight in females only, is uncertain (Kirk et al. 1990). In B6C3F1 mice and hamsters, gavage doses of ≥125 mg/kg/day for 4 weeks (5 days/week) resulted in mild to moderate fatty changes in both species and increased liver weight in mice; mice also showed increased serum total cholesterol and triglycerides at 250 mg/kg/day (Gi et al. 2015a). In contrast, NTP (1986) did not report any exposure-related hepatic lesions in B6C3F1 mice exposed to gavage doses up to 500 mg/kg/day for 13 weeks (5 days/week) (NTP 1986).

In the chronic study by NTP (1986), liver necrosis was observed in female rats exposed to gavage doses of 250 mg/kg/day for 103 weeks (5 days/week), but not in females or males exposed to 125 mg/kg/day. The chronic NTP study (1986) also reported necrosis of the liver in male mice similarly exposed to 250 mg/kg/day, but not in males at 125 mg/kg/day, or in females at either dose.

Mechanisms of Hepatotoxicity. Data regarding mechanisms of hepatotoxicity following exposure to 1,2-dichloropropane are limited. A proposed mechanism of general toxicity is glutathione depletion due to glutathione-conjugation of reactive metabolites (Di Nucci et al. 1988; Imberti et al. 1990). Glutathione depletion has been observed in the liver following acute oral or intraperitoneal exposure (Di Nucci et al. 1988, 1990; Imberti et al. 1990; Trevisan et al. 1989, 1991), and Imberti et al. (1990) have shown a

statistically significant association between glutathione depletion in the liver and altered clinical chemistry parameters. If a glutathione precursor (N-acetylcysteine) is administered prior to 1,2-dichloropropane, the extent of liver injury is decreased. Oxidation of 1,2-dichloropropane by CYP2E1 prior to glutathione-conjugation appears to be an important step in hepatotoxicity (Gi et al. 2015a; Yanagiba et al. 2016). In CYP2E1-null mice, intraperitoneal injections of 1,2-dichloropropane did not cause hepatotoxic effects in similarly exposed wild-type mice (Yanagiba et al. 2016). Additionally, treating mice with a CYP450 inhibitor during intermediate-duration inhalation exposure to 1,2-dichloropropane attenuated the compound-induced proliferation of cholangiocytes and hepatocytes, apoptosis of cholangiocytes, and induction of proteins associated with catalytic and carboxylic ester hydrolase activities (Zhang et al. 2018, 2020). Based on intraperitoneal injection experiments, Trevisan et al. (1989) proposed that with repeated exposure, adaptive mechanisms in the liver may compensate for glutathione depletion, resulting in decreased liver toxicity. This is consistent with findings in oral and inhalation studies, which generally observed hepatic effects at lower exposure levels following acute- or intermediate-duration exposures than observed with chronic exposures.

Wang et al (2019) proposed mitochondrial dysfunction in hepatocytes following exposure to 1,2-dichloropropane as a possible mechanism of hepatotoxicity. In mice, inhalation of 1,2-dichloropropane at 300 ppm for 6 hours resulted in inhibition of the mitochondrial electron transport chain complex activities, resulting in mitochondrial dysfunction and increased ATP consumption. The study authors proposed that this decrease in ATP consumption leads to hepatic necrosis. ATP depletion inhibits mitochondrial cytochrome c release. Since release of mitochondrial cytochrome c triggers apoptosis, decreased mitochondrial cytochrome c release inhibits cell apoptosis. Therefore, excessive ATP depletion can result in inhibition of the apoptotic death pathway, leading to cell death via necrosis. Exposure also reduced the activity of microsomal glutathione S-transferase, a key enzyme in the mitochondria that protects against oxidative stress.

2.10 RENAL

Based on several case reports of occupational exposure, accidental or intentional ingestion, or intentional inhalation abuse (“sniffing” or “huffing”) of large amounts of mixtures containing 1,2-dichloropropane, the kidney is a target for the toxic effects of 1,2-dichloropropane (Di Nucci et al. 1988; Perbellini et al. 1985; Pozzi et al. 1985; see also ACGIH 2014; EPA 2016a; IARC 1986, 2017). Effects associated with exposure included impaired kidney function, tubular necrosis, and acute kidney failure. Recovery was complete in nonfatal cases. Acute renal failure, characterized by increased serum creatinine and blood

urea nitrogen (BUN), hyperkalemia, and oliguria, was reported in a 43-year-old man 4 days after a prolonged dermal exposure (~5 hours) to a commercial fixative containing 30–40% 1,2-dichloropropane and 33–38% toluene; the patient made a full recovery within 2 weeks (Fiaccadori et al. 2003). Exact exposure levels cannot be determined in these case studies, so a LOAEL cannot be determined.

Inconsistent findings of kidney damage were observed following inhalation exposure to 1,2-dichloropropane in laboratory animals, and no histopathological lesions of the kidney were associated with oral exposure to 1,2-dichloropropane in any of the species evaluated.

Inhalation Exposure. No exposure-related changes in kidney histology were observed in rats or mice exposed to 1,2-dichloropropane at concentrations up to 1,500 ppm for 6 hours, rats or rabbits exposed to concentrations up to 1,000 ppm for up to 2 weeks (6–7 hours/day, 4–5 days/week), or mice exposed to concentrations up to 300 ppm for 2 weeks (6 hours/day, 4–5 days/week) (Nitschke and Johnson 1983). Similarly, no exposure-related histopathologic effects on the kidneys were observed in 13-week studies (6 hours/day, 5 days/week) in rats exposed to concentrations up to 2,000 ppm, mice exposed to concentrations up to 400 ppm, or rabbits exposed to concentrations up to 1,000 ppm (Matsumoto et al. 2013; Nitschke et al. 1988; Umeda et al. 2010). However, older studies reported fatty degeneration in the kidney in acute-duration studies at concentrations of 2,200 ppm in rats and guinea pigs, ≥1,600 ppm in rabbits, and ≥1,000 ppm in mice (Heppel et al. 1946a, 1948; Highman and Heppel 1946). Similar effects were noted in older intermediate-duration studies in rats and guinea pigs at 1,500 ppm, mice at 400 ppm, and dogs at 1,000 ppm; no changes in kidney histology were observed in rabbits at acute- or intermediate-duration concentrations up to 1,500 ppm (Heppel et al. 1946a, 1948; Highman and Heppel 1946).

In chronic studies, no exposure-related histopathologic effects on the kidneys were observed in rats exposed to concentrations up to 500 ppm (Matsumoto et al. 2013; Umeda et al. 2010) or female mice exposed to concentrations up to 200 ppm for 104 weeks (5 days/week, 6 hours/day). However, increased kidney weight and basophilic changes and cortical mineralization were observed in male mice at all tested concentrations (≥32 ppm) (Matsumoto et al. 2013).

Oral Exposure. No histopathologic changes in the kidneys were observed following acute gavage exposure to 1,2-dichloropropane in rats at doses up to 1,000 mg/kg/day (Bruckner et al. 1989; Gorzinski and Johnson 1989), mice at doses up to 500 mg/kg/day (Gi et al. 2015a), rabbits at doses up to 500 mg/kg/day (Kirk et al. 1988), or hamsters at TWA doses up to 333 mg/kg/day (500 mg/kg/day for 1 day followed by 250 mg/kg/day for 2 days) (Gi et al. 2015a). However, the rabbit study (Kirk et al.

1988) was considered inadequate due to low animal numbers per group (n=2). While no histopathological effects were observed, serum BUN levels were elevated by 1.5–2-fold in rats treated with 1,000 mg/kg/day for 5 or 10 days (Bruckner et al. 1989). Imberti et al. (1990) also reported a significant 2–3-fold increase in serum urea levels in rats 24 and 98 hours after a single administration of 2,000 mg/kg/day (only dose tested); however, increases in serum urea levels at 48 hours were not significant. Due to limited endpoint evaluation (no assessment of kidney weight or histology) and lack of consistency across time points, renal endpoints from the study by Imberti et al. (1990) were not included in the LSE tables or figures.

Other acute studies evaluated limited renal endpoints, but they were not included in the LSE tables or figures due to lack of histological examinations. In a 2-week NTP study (1986), gross pathologic examinations showed reddened renal medullae in almost all rats that were treated with 2,000 mg/kg/day by gavage for 2 weeks. This effect was also observed in mice that were similarly treated at doses ≥125 mg/kg/day. Histological examinations were not performed. NTP (1986) considered the reddened medullae to be a compound-related, but not an adverse effect. No changes in maternal kidney weight were observed in pregnant rats exposed to gavage doses up to 500 mg/kg/day on GDs 6–15, or pregnant rabbits exposed to gavage doses up to 250 mg/kg/day on GDs 7–19 (Berdasco et al. 1988; Kirk et al. 1989, 1995); serum chemistry and histology were not assessed.

In longer-duration studies, no exposure-related histopathological kidney lesions were observed following intermittent gavage exposure (5 days/week) in mice or hamsters at doses up to 250 mg/kg/day for 4 weeks (Gi et al. 2015a), in rats at doses up to 1,000 mg/kg/day for 13 weeks (Bruckner et al. 1989; NTP 1986), in mice at doses up to 500 mg/kg/day for 13 weeks (NTP 1986), or in rats or mice treated with gavage doses up to 250 mg/kg/day for 103 weeks (NTP 1986). Exposure-related kidney lesions were not observed in a 2-generation study in F0 or F1 adult rats exposed to drinking water concentrations up to 0.24% (estimated doses of 152–293 mg/kg/day per sex per generation) for 13–21 weeks (Kirk et al. 1990).

Mechanisms of Renal Toxicity. Data regarding mechanisms of toxicity following exposure to 1,2-dichloropropane are limited. Imberti et al. (1990) proposed that glutathione depletion may contribute to toxicity because a statistically significant association between glutathione depletion in the kidney (and liver) and altered clinical chemistry parameters were observed following acute oral exposure to 1,2-dichloropropane. If a glutathione precursor (N-acetylcysteine) is administered prior to 1,2-dichloro-propane, the extent of kidney injury is decreased.

Odinecs et al. (1995) suggested that males may be more susceptible to renal toxicity following exposure to 1,2-dichloropropane due to sex-specific differences in CYP2E1 expression in the kidney. Differential expression appears to be mediated by testosterone levels. As discussed in Section 2.9 (Hepatic), oxidation of 1,2-dichloropropane by CYP2E1 prior to glutathione conjugation appears to be an important step in hepatotoxicity (Gi et al. 2015a; Yanagiba et al. 2016). Data from Odinecs et al. (1995) suggested that this is also an important step for renal toxicity. In support, glutathione depletion and cytotoxicity following *in vitro* exposure to 1,2-dichloropropane were significantly higher in renal slices from male rats compared with female rats (Trevisan et al. 1992).

2.11 DERMAL

Allergic contact dermatitis has been reported in case studies of humans following chronic occupational exposure to mixtures containing 1,2-dichloropropane; skin symptoms generally resolved following cessation of exposure (Baruffini et al. 1989; Grzywa and Rudzki 1981). Patch testing for reactions to 1,2-dichloropropane was positive in all 12 cases evaluated (Baruffini et al. 1989; Grzywa and Rudzki 1981). In the general population without occupational exposure to 1,2-dichloropropane, only 2/12 subjects showed slight skin erythema in patch testing (Baruffini et al. 1989). Transient skin reddening was reported in a 43-year-old man after a prolonged dermal exposure (~5 hours) to a commercial fixative containing 30–40% 1,2-dichloropropane and 33–38% toluene (Fiaccadori et al. 2003).

Reddened and inflamed skin were observed in rats following exposure to 2.34 g/kg for 24 hours in occluded conditions (Shell Oil Co. 1982). In a 24-hour Draize occlusive patch test, mild skin irritation was observed in male rabbits, and extreme skin irritation (chemical burns, superficial necrosis) was observed in female rabbits following exposure to 1.16 g/mL; skin effects were still evident in both sexes 21 days later, including hardening and lifting of skin in female rabbits (Shell Oil Co. 1982). The cause for the differential effects in males and females is unknown. Following repeated application of 1,2-dichloropropane to the dorsal skin of the ear for 7 days, dermatitis and angiogenesis were observed in mice at doses≥2.73 mL/kg (Jin et al. 2019). Inflammatory markers (IL-6 and TNF-alpha) and an angiogenesis marker (VEGF) were elevated in the skin in a dose-related manner. Shell Oil Co. (1982) also determined that 1,2-dichloropropane is a strong skin sensitizer in guinea pigs at 0.56 g/mL.

No treatment-related skin lesions were observed histologically in rats and mice exposed to air concentrations of 1,2-dichloropropane up to 150 ppm, or rabbits exposed to concentrations up to 1,000 ppm, 6 hours/day, 5 days/week for 13 weeks (Nitschke et al. 1988). No treatment-related skin lesions were observed histologically in rats or mice treated with 1,2-dichloropropane by gavage 5 days/week at doses up to 1,000 mg/kg/day for 13 weeks (NTP 1986), or 250 mg/kg/day for 103 weeks (NTP 1986).

2.12 OCULAR

Periorbital and conjunctival hemorrhages were seen in a patient who was admitted to a hospital after exposure to vapors of 1,2-dichloropropane (Pozzi et al. 1985). It was not clear if the hemorrhages resulted from inhalation of 1,2-dichloropropane or from direct exposure of the eye to the 1,2-dichloropropane vapor. No concentration information was provided.

1,2-Dichloropropane is an eye irritant in rabbits. Initial pain, redness, iridial irritation, and corneal ulceration were observed following direct ocular instillation of undiluted 1,2-dichloropropane (Exxon 1981c; Shell Oil Co. 1982). All animals recovered within 7–14 days. Conjunctivitis was observed in guinea pigs following acute inhalation exposure to 2,200 ppm (7 hours) (Heppel et al. 1946a).

No adverse effects on the eye were found following gross and histopathologic examination of rats and mice exposed to air concentrations of 1,2-dichloropropane up to 150 ppm, or rabbits exposed to concentrations up to 1,000 ppm for 13 weeks (6 hours/day, 5 days/week) (Nitschke et al. 1988). No exposure-related effects were observed in ophthalmological examinations conducted before and after drinking water exposure in F0 rats in a 2-generation study by Kirk et al. (1990). F0 males were exposed to doses up to 152 mg/kg/day for 10–12 weeks prior to mating through mating, and F0 females were exposed to doses up to 254 mg/kg/day for 10–12 weeks prior to mating through lactation.

2.13 ENDOCRINE

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

Inhalation and oral exposure studies in laboratory animals show inconsistent evidence of histopathological effects in the adrenal glands following exposure to very high levels of 1,2-dichloropropane associated with mortality. No histopathological changes were observed in other endocrine organs

(thyroid, parathyroids, pancreas, pituitary gland) in exposed laboratory animals. Although some reproductive organs have endocrine functions, all reproductive organ effects are discussed in Section 2.16 (Reproductive).

Inhalation Exposure. Histopathological changes in the adrenal glands were observed following 1–8 exposures to 2,200 ppm (7 hours/exposure), including depletion of the lipoid material of the adrenal cortex in rats and adrenal necrosis in guinea pigs (Heppel et al. 1946a; Highman and Heppel 1946). Similar effects were noted in a limited number of dogs exposed to 1,000 ppm (7 hours/day, 5 days/week) for up to 96 exposures (Heppel et al. 1946a). Fatty changes were observed in the adrenal glands of female rats, but not male rats, following exposure to 2,000 ppm for 13 weeks (6 hours/day, 5 days/week) (Umeda et al. 2010). No adrenal gland changes were observed in rats following exposure to concentrations up to 1,000 ppm for 2 or 13 weeks (Nitschke and Johnson 1983; Nitschke et al. 1988; Umeda et al. 2010), or up to 500 ppm for 104 weeks (Umeda et al. 2010). In mice, no histopathological changes in the adrenal glands were observed following intermittent exposure (6 hours/day, 4–5 days/week) to concentrations up to 300 ppm for 2 weeks (Nitschke and Johnson 1983), 400 ppm for 13 weeks (Matsumoto et al. 2013; Nitschke et al. 1988), or 200 ppm for 104 weeks (Matsumoto et al. 2013). Additionally, no histopathological changes in the adrenal glands were observed in rabbits following intermittent exposure (6 hours/day, 5 days/week) to concentrations up to 1,000 ppm for 2 weeks (Nitschke and Johnson 1983), or 150 ppm for 13 weeks (Nitschke et al. 1988).

No histopathological changes were reported in the thyroid, parathyroids, pancreas, or pituitary gland in rats, mice, or rabbits following exposure to concentrations as high as 2,000 ppm for 13 weeks, or 500 ppm for 104 weeks (6 hours/day, 5 days/week) (Matsumoto et al. 2013; Nitschke et al. 1988; Umeda et al. 2010).

Oral Exposure. Increased fat deposition in the adrenal glands was observed in male rats exposed to gavage doses of ≥500 mg/kg/day for 13 weeks (5 days/week); vacuolization of the adrenal medulla and lipidosis of the adrenal cortex were also observed in Sprague-Dawley male rats exposed to 750 mg/kg/day and sacrificed moribund on day 10 (Bruckner et al. 1989). No fatty changes were observed in the adrenal glands of similarly exposed females or male or female rats exposed to gavage doses up to 1,000 mg/kg/day for 1–10 days (Bruckner et al. 1989). In F344 rats, no histopathological alterations were observed in the adrenal glands of males or females exposed to gavage doses up to 1,000 mg/kg/day for 13 weeks, or 250 mg/kg/day for 103 weeks (5 days/week) (NTP 1986). No histopathological changes

were observed in male or female mice following gavage doses up to 500 mg/kg/day for 13 weeks or 250 mg/kg/day for 103 weeks (5 days/week) (NTP 1986).

No histopathological changes were observed in the thyroid, parathyroids, pancreas, or pituitary gland in rats or mice following gavage doses up to 1,000 mg/kg/day for 13 weeks, or 250 mg/kg/day for 103 weeks (5 days/week) (NTP 1986).

2.14 IMMUNOLOGICAL

As reported in the Section 2.11 (dermal), allergic contact dermatitis with positive patch testing has been reported in case-studies of humans following chronic occupational exposure to mixtures containing 1,2-dichloropropane; skin symptoms generally resolved following cessation of exposure (Baruffini et al. 1989; Grzywa and Rudzki 1981). Mild reactions were only observed in patch testing of 2/120 subjects who did not have prior occupational exposure to 1,2-dichloropropane (Baruffini et al. 1989). In a case-control study in South Korea, Choi et al. (2009) did not find a significant difference in indoor and outdoor residential air levels of 1,2-dichloropropane between individuals with dermatitis (n=50) or asthma (n=36) and control subjects (n=28); 34 VOCs were measured in this study. No additional information regarding the potential for immunological effects in humans following exposure to 1,2-dichloropropane were available.

As reported in Section 2.11 (dermal), 1,2-dichloropropane is a strong skin sensitizer in guinea pigs (Shell Oil Co. 1982). No additional parameters of immunological function have been directly assessed following exposure to 1,2-dichloropropane in any available laboratory animal study. Immune system evaluation in additional studies is limited to organ weight and/or histology, without evaluation of potential effects on immunological function.

Most inhalation studies did not observe exposure-related weight or histopathological changes in the thymus following intermediate exposure in rats, mice, and rabbits at concentrations up to 2,000 ppm (Matsumoto et al. 2013; Nitschke et al. 1988; Umeda et al. 2010), or chronic exposure in rats or mice at concentrations up to 500 ppm (Matsumoto et al. 2013; Umeda et al. 2010). However, a decrease in the absolute and relative thymus weight and a decrease in cortical lymphoid cells were observed in mice exposed to 300 ppm 6 hours/day, 4–5 days/week, for 2 weeks (Nitschke and Johnson 1983).

No treatment-related histopathological lesions were observed in the thymus of rats or mice exposed 5 days/week via gavage doses up to 1,000 mg/kg/day for 13 weeks or up to 250 mg/kg/day for 103 weeks (NTP 1986). Reduced survival of the high-dose female mice in the 103-week study may have been partly due to infections of the reproductive system, as inflammation of the reproductive system was observed in many of the animals that died during the study (5/11 controls, 9/14 at 125 mg/kg/day, and 14/22 at 250 mg/kg/day). However, available data is inadequate to determine if 1,2-dichloropropane caused an increased susceptibility to the infection observed in this study.

Histopathological lesions observed in the spleen and bone marrow following inhalation and oral exposure to 1,2-dichloropropane are secondary to hemolytic anemia (e.g., elevated spleen weight, hemosiderin deposits, increased hematopoiesis) rather than immunotoxicity; see Section 2.7 (Hematological) for more information. Evidence of splenic tumors following chronic exposure to 1,2-dichloropropane is discussed in Section 2.19 (Cancer).

2.15 NEUROLOGICAL

As expected with high-level solvent exposure, severe CNS depression and coma have been reported in cases of accidental or intentional ingestion or intentional inhalation abuse (“sniffing” or “huffing”) of large amounts of mixtures containing 1,2-dichloropropane (Larcan et al. 1977; Perbellini et al. 1985; see also reviews by ACGIH 2014; EPA 2016a; IARC 2017). Rubin (1988) also reported fatigue, possibly attributable to CNS depression, in people who were exposed to unknown concentrations of 1,2-dichloropropane from a tank truck that leaked 2,000 gallons of the chemical. Exact exposure levels cannot be determined in these case studies, so a LOAEL cannot be determined.

An occupational case study reported dizziness, headache, double vision, nausea and vomiting, and ataxia in a Korean worker exposed to 1,2-dichloropropane over the course of 7 work days in June 2017 while removing rust from inside cleaning trays of an ultrasonicator that used 1,2-dichloropropane as a detergent to clean automotive parts; the worker did not wear provided personal protective equipment (Kwak et al. 2018). Symptoms improved over the weekend but worsened during the workday, and CNS effects did not reoccur once the worker was reassigned to a job without exposure to detergents or organic solvents. Time-weighted air levels in the automotive accessory manufacturing plant ranged from 8.4 ppm in June 2017 to 26.9–41.5 ppm in September 2017; peak measurements taken during rust removal ranged from 49.8 to 76.6 ppm in September 2017. The time spent engaged in rust removal over the course of a workday was not reported.

1,2-Dichloropropane is a CNS depressant in animals at high exposure levels via inhalation and oral routes. There is no evidence that exposure leads to damage of CNS tissues.

Inhalation Exposure. Mild CNS depression (drowsiness, listlessness, incoordination) was observed in rats, mice, and guinea pigs during 7-hour exposures to concentrations ≥1,000 ppm, with gross motor incoordination and prostration at 2,200 ppm (Heppel et al. 1946a). Animals became less susceptible to CNS depression with repeated exposures. CNS depression has been observed following 6-hour inhalation exposure to 1,2-dichloropropane in both mice and rats (Nitschke and Johnson 1983). Anesthesia was observed in rats at 1,500 ppm. In mice, lethargy was observed at ≥500 ppm, with lethal CNS depression at 1,500 ppm.

Sidorenko et al. (1976) described the sequence of signs of intoxication in mice that were acutely exposed by inhalation to 1,2-dichloropropane. General agitation and decreased coordination of movements occurred initially, followed by sluggishness, amyotonia, and sporadic clonic spasms, and subsequently by loss of righting reflex. The loss of the righting reflex occurred at the lowest concentration given (1,000 ppm). Sidorenko et al. (1979) evaluated the neurological effects in rats resulting from acute and intermediate duration exposure to 1,2-dichloropropane. A total threshold indicator (TTI) was used to assess the effects on the CNS, but the details of the TTI were not explained in the study. In addition, control data and numbers of treated rats and mice were not reported. Due to these inadequacies, these studies were not included in the LSE tables or figures.

No overt signs of neurotoxicity, changes in brain weight, or exposure-related lesions in nervous system tissue were reported in rats or mice intermittently exposed (6 hours/day, 5 days/week) to concentrations up to 2,000 or 400 ppm, respectively, for 13 weeks, or 500 or 200 ppm, respectively, for up to 103 weeks (Masumoto et al. 2013; Nitschke et al. 1988; Umeda et al. 2010). No overt signs of neurotoxicity or exposure-related lesions in nervous system tissue were reported in rabbits similarly exposed to concentrations up to 1,000 ppm for 13 weeks (Nitschke et al. 1988). No tests of neurological function or behavioral assays were conducted in these studies.

Oral Exposure. Three studies were specifically designed to assess neurobehavior following acute oral exposure to 1,2-dichloropropane. In both 2- and 13-week neurotoxicity studies, transient mild clinical signs (blinking, lacrimation, salivation) were observed in rats following gavage administration for 3–4 days, but not during the remainder of the study duration (Gorzinski and Johnson 1989; Johnson and

Gorzinski 1988). A trend toward reduced locomotion was reported at ≥300 mg/kg/day in the 2-week study (Gorzinski and Johnson 1989). The 13-week study reported no exposure-related changes in monthly assessments of neurological function (functional observation battery, hindlimb grip strength, motor activity) at doses up to 200 mg/kg/day; based on the lack of effects in behavioral testing, a NOAEL of 200 mg/kg/day was established for neurological effects following repeated exposure (Johnson and Gorzinski 1988). In a gestational exposure study, adverse effects observed during an observational battery in pregnant rats exposed via gavage on GDs 6–21 included decreased movement, muscle tone, and extensor thrust reflex, and increased salivation and lacrimation at 125 mg/kg/day, but not ≤30 mg/kg/day (Kirk et al. 1995).

Clinical signs of neurotoxicity were observed in other oral studies that were not specifically designed to evaluate neurological function or behavior. Dose-related increases were noted in CNS depression in rats following gavage doses ≥100 mg/kg/day for 1–10 consecutive days, with transient effects at lower doses and prolonged and/or severe depression at ≥500 mg/kg/day (Bruckner et al. 1989; Exxon 1981a; Kirk et al. 1989; Shell Oil Co. 1982). CNS depression was also reported in rabbits following gavage doses ≥500 mg/kg/day for 13 consecutive days (Kirk et al. 1988); however, this study is considered inadequate due to low animal numbers per group (n=2). In an intermediate-duration study, Bruckner et al. (1989) also observed pronounced CNS depression in rats treated with 500 mg/kg/day by gavage for 13 weeks (5 days/week). No CNS depression was reported at doses up to 250 mg/kg/day; it is unclear if no effects were observed, or if effects were not reported due to the expected transient nature of effects at doses <500 mg/kg/day (based on observations in acute studies).

No histopathologic lesions were found in the brain of rats at doses up to 1,000 mg/kg/day for up to 13 weeks (Bruckner et al. 1989; Johnson and Gorzinski 1988; NTP 1986); mice at doses up to 500 mg/kg/day for 13 weeks (NTP 1986); or rats and mice at doses up to 250 mg/kg/day for 103 weeks (NTP 1986).

2.16 REPRODUCTIVE

Pozzi et al. (1985) reported the case of a woman who was hospitalized with metrorrhagia (bleeding from the uterus between menstrual periods) after acute inhalation of 1,2-dichloropropane. The metrorrhagia was a transient effect. No information regarding concentration was given. No additional information regarding the potential for reproductive system effects in humans following exposure to 1,2-dichloropropane were available.

The reproductive system does not appear to be a sensitive target of 1,2-dichloropropane toxicity in laboratory animals.

Inhalation Exposure. No inhalation studies evaluating the potential for 1,2-dichloropropane to alter reproductive capability in laboratory animals were available. However, Sekiguchi et al. (2002) observed that exposure to 1,2-dichloropropane for approximately 3 weeks (8 hours/day) significantly increased the incidence of lengthened estrous cycles (≥6 days) in nulliparous female rats at ≥100 ppm and decreased ovulation at 200 ppm; no changes in the estrous cycle or ovulation were observed at 50 ppm. No exposure-related changes in the weight of the ovaries or uterus were observed; organs were not examined for histopathological lesions, and fertility was not assessed (Sekiguchi et al. 2002).

Several inhalation studies reported a lack of exposure-related histopathological changes in reproductive organs following exposure to 1,2-dichloropropane; however, they did not assess reproductive function. In 2-week studies (6 hours/day, 4–5 days/week), no histopathological changes were observed in the testes of rats, mice, or rabbits exposed to concentrations up to 1,000, 300, or 1,000 ppm, respectively (Nitschke and Johnson 1983). In intermediate- and chronic-duration studies (6 hours/day, 5 days/week), no histological changes were observed in reproductive organs in rats at ≤2,000 ppm for 13 weeks or ≤500 ppm for up to 104 weeks (Nitschke et al. 1988; Umeda et al. 2010), mice at ≤400 ppm for 13 weeks or ≤200 ppm for up to 104 weeks (Matsumoto et al. 2013; Nitschke et al. 1988), or rabbits at ≤1,000 ppm for 13 weeks (Nitschke et al. 1988).

Oral Exposure. Reproductive endpoints have been assessed following oral exposure to 1,2-dichloropropane in a 2-generation drinking water study in rats and gestational gavage studies in rats and rabbits. In the 2-generation study, there were no exposure-related changes in mating, fertility, or litter indices in either generation at drinking water concentrations up to 0.24% (estimated doses ranged from 152 to 293 mg/kg/day per sex per generation); additionally, no exposure-related changes in reproductive organ histology were observed in parental animals (Kirk et al. 1990). Similarly, in gestational studies, no dose-related effects on the number of corpora lutea, number of implantation sites, number of resorptions, gravid uterine weight, or number of live and dead fetuses were found at doses up to 500 mg/kg/day in rats exposed on GDs 6–21, or 150 mg/kg/day in rabbits exposed on GDs 7–19 (Kirk et al. 1989; 1995). In a dose-range finding study, complete litter resorption was observed in 2/5 surviving rabbit does at 250 mg/kg/day; however, this dose was associated with maternal toxicity (2/7 maternal deaths) (Berdasco et al. 1988).

In a series of studies in Sprague-Dawley male rats, Bruckner et al. (1989) reported testicular degeneration in males treated with gavage doses ≥500 mg/kg/day for 10 consecutive days or for 13 weeks (5 days/week). The degeneration included reduced sperm production, increased numbers of degenerate sperm, and reduced numbers of sperm in the epididymis. However, no exposure-related changes were observed in the testes of F344 rats similarly exposed to doses up to 1,000 mg/kg/day for 13 weeks (NTP 1986). No testicular effects were observed in rats of either strain exposed to doses up to 1,000 mg/kg/day for 1–5 days, or up to 250 mg/kg/day for 10 days, 13 weeks, or 103 weeks (Bruckner et al. 1989, NTP 1986). In male mice, no exposure-related histopathological lesions were observed in male reproductive organs following exposure to doses up to 500 mg/kg/day for 13 weeks, or 250 mg/kg/day for 103 weeks (NTP 1986). Reproductive function was not assessed in these studies.

No exposure-related histopathological changes were observed in female reproductive organs in rats exposed to gavage doses up to 1,000 mg/kg/day for 13 weeks (5 days/week); however, rats exposed to ≥250 mg/kg/day for up to 103 weeks had significantly increased incidences of mammary gland hyperplasia and mammary tumors (NTP 1986); see more details in Section 2.19 (Cancer). In female mice, increased incidences of suppurative infection of the ovary, uterus, or other organs were observed following exposure to gavage doses of 125 and 250 mg/kg/day for 103 weeks (5 days/week); however, it is not known if these infections were related to 1,2-dichloropropane treatment since controls were also infected (NTP 1986). Reproductive function was not assessed in these studies.

2.17 DEVELOPMENTAL

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

The potential for developmental effects in laboratory animals has been assessed via the oral route only. In gestational studies, an increased incidence of delayed ossification of the bones of the skull was observed in the fetuses of rat dams exposed to 125 mg/kg/day via gavage on GDs 6–21, and rabbit does exposed to 150 mg/kg/day via gavage on GDs 7–19 (Kirk et al. 1995). In both species, maternal toxicity occurred at the fetotoxic dose, including clinical signs (CNS depression, salivation, and lacrimation) and decreased body weight in rat dams, and anorexia and anemia in rabbit does (Kirk et al. 1995). No maternal toxicity or fetal effects were observed at doses up to 30 mg/kg/day in rats, or 50 mg/kg/day in rabbits, and no

evidence of embryotoxic effects or increased incidences of malformations were observed at any dose. Observed fetotoxicity may be secondary to maternal toxicity in both species.

In a 2-generation study, decreased neonatal survival and reduced neonatal body weights were observed in the F1 offspring following parental exposure to a drinking water concentration of 0.24% (estimated doses of 152–254 mg/kg/day) prior to mating through lactation (Kirk et al. 1990). Parental toxicity was also observed at this dose (decreased body weight, maternal anemia, hepatic toxicity); therefore, observed neonatal effects may be secondary to parental toxicity. No parental or offspring toxicity was observed at lower concentration levels ≤0.10% (estimated doses 83–127 mg/kg/day), and no external malformations were observed at any dose (offspring were not assessed for skeletal or visceral malformations or variations).

2.18 OTHER NONCANCER

Studies evaluating potential other noncancer effects following exposure to 1,2-dichloropropane in humans or animals were not located.

2.19 CANCER

A series of case reports and retrospective cohort studies from Japanese printing companies indicate that exposure to 1,2-dichloropropane (and/or other chlorinated solvents) may increase the risk of developing cholangiocarcinoma (CCA), a rare form of bile duct cancer (Kinoshita et al. 2019; Kubo et al. 2013, 2014a, 2014b; Kumagai 2014; Kumagai et al. 2013, 2014, 2016; Nakagawa et al. 2015; Ogawa et al. 2020; Sobue et al. 2015; Tomimaru et al. 2015; Yamada et al. 2014, 2015a, 2015b). The case-series reports and cohort studies are discussed below; additional details can be found in Table 2-4.

Initial studies focused on a cluster of CCA cases in male print shop workers from Osaka, Japan (Kubo et al. 2014a; Kumagai et al. 2013, 2014, 2016; Sobue et al. 2015). In all, 17 cases were diagnosed between 1996 and 2012, 9 of which were fatal. None of the workers had known risk factors for developing CCA (e.g., primary sclerosing cholangitis, hepatolithiasis, pancreaticobiliary maljunction, or infection with liver flukes), and all were below the average age of diagnosis in Japan (65.5 years of age) (Kubo et al. 2014a). Based on work history, all 17 cases were exposed to 1,2-dichloropropane, 11/17 cases were exposed to dichloromethane, and 8/17 cases were exposed to 1,1,1-trichloroethane (Kubo et al. 2014a; Kumagai et al. 2016; Sobue et al. 2015). No air monitoring data were available; however, using exposure estimates based on reported chemical quantities used per year, estimated 1,2-dichloropropane air levels

Table 2-4. Cholangiocarcinoma (CCA) in Humans Exposed to 1,2-Dichloropropane

Reference and study population	Exposure	Outcomes
Occupational studies from a printing company based in Osaka, Japan		
Kumagai et al. 2013, 2014 Retrospective cohort study of print shops in Osaka, Japan; 51 male printers and 11 male workers from adjacent front room employed between 1991 and 2006 Employment duration: 1–17 years (mean 10 years)	**Exposure:** Exposure estimates were generated based on amounts of the chemicals reportedly used between 1991 and 2006 using experimental data generated by JNIOSH 1,2-DCP (used from 1991–2006): Print-shop: 190–310 ppm Front-room: 70–110 ppm DCM (used from 1991 to 1997/1998): Print-shop: 140–360 ppm Front-room: 50–130 ppm	**Cancer effect:** CCA observed in 11/51 printers (22%) and 0/11 front-room workers 11/11 cases were exposed to 1,2-DCP 10/11 cases were exposed to DCM SMR (95% CI) for CCA among 1,2-DCP-exposed workers (using national incidence): 2,900 (1,100–6,400)
Kubo et al. 2014a Case-series report of 17 male print shop workers diagnosed with CCA between 1996 and 2012 in Osaka, Japan; all printers were employed at the printing company described by Kumagai et al. (2013, 2014) Employment duration: 6–19 years (mean 11 years)	**Exposure:** Exposure to 1,2-DCP, DCM, and TCE was determined based on job history; no exposure estimates were calculated 1,2-DCP (used from 1991 to 2006) DCM (used from 1991 to 1996) TCE (used from 1991 to 1992)	**Cancer effect:** Based on employment records, estimated CCA incidence from 1981 to 2012 was 17/111 (15%) Based on job history: 17/17 cases exposed to 1,2-DCP 11/17 cases exposed to DCM 8/17 cases exposed to TCE
Sobue et al. 2015 Retrospective cohort study of print shop in Osaka, Japan; 86 male and 20 female workers employed between 1985 and 2012; all printers were employed at the printing company described by Kumagai et al. (2013, 2014, 2016) and Kubo et al. (2014a)	**Exposure:** Exposure to 1,2-DCP and DCM was determined based on job history; no exposure estimates were calculated 1,2-DCP (used from 1991 to 2006) DCM (used from 1991 to 1996) Note: Exposure to TCE expected from 1985-1992 based on report by Kubo et al. (2014a) and Kumagai et al. (2016)	**Cancer effect:** CCA incidence was 17/106 (16%); same cases initially described by Kubo et al. (2014a) SIR (95% CI) for CCA among 1,2-DCP-exposed workers All workers: 1,319.9 (658.9–2,361.7) Male workers 1,163.2 (677.6–1,862.4)

Table 2-4. Cholangiocarcinoma (CCA) in Humans Exposed to 1,2-Dichloropropane

Reference and study population	Exposure	Outcomes
Employment duration: 1–16 years (1,452.4 total person-years of exposure)		Workers exposed to 1,2-DCP only: 1,002.8 (368.0–2182.8) Workers exposed to 1,2-DCP + DCM: 1,319.9 (658.9–2361.7)
Kumagai et al. 2016 Retrospective cohort study of three print shops in Osaka, Japan and one print shop in Tokyo, Japan (all run by the same company; only Osaka Plant 2 currently operational); 78 male workers and 17 female workers employed between 1985 and 2006 (71 printers, 20 front room workers, 4 delivery workers); some workers were employed in multiple plants during working history Employment duration: Employment duration not reported; median (range) exposure to 1,2-DCP was reported as 3.3 years (0.3–15.1 years)	**Exposure:** Exposure estimates were generated based on amounts of the chemicals reportedly used between 1985 and 2006 using experimental data generated by JNIOSH Printers: November 1987–February 1996 (Osaka Plants 1 and 2) 1,2-DCP: 130–210 ppm DCM: 65–170 ppm March 1996–October 2006 (Osaka Plants 2 and 3; Tokyo Plant) 1,2-DCP: 84–346 ppm Front room workers: April 1991–February 1996 (Osaka Plant 2) 1,2-DCP: 51–76 ppm DCM: 45–100 ppm March 1996–October 2006 (Osaka Plant 2; Tokyo Plant) 1,2-DCP: 55–130 ppm Workers were also exposed to TCE in Osaka Plants 1 and 2 until 1992 (exposure estimates not reported).	**Cancer effect:** CCA incidence was 17/95 (18%); same cases initially described by Kubo et al. (2014a); all cases were men SIR (95% CI) for CCA among 1,2-DCP-exposed workers All workers (n=95): 1,171 (682–1,875) Male workers (n=78): 1,203 (701–1,927) Workers exposed to 1,2-DCP only (n=62): 1,019 (374–2,218) Workers exposed to 1,2-DCP + DCM (n=33): 1,275 (636–2,280) RR (95% CI) of CCA per tertile increase in cumulative exposure to 1,2-DCP (ppm-years; lag=0) Tertile 1 (1–1,599) 1 (Referent) Tertile 2 (1,600–2,399) 14.9 (4.1–54.3) Tertile 3 (2,400–3,499) 17.1 (3.8–76.2) RR (95% CI) of CCA per inter-tertile increase in cumulative exposure to 1,2-DCP (ppm-years; lag=5 years) Tertile 1 (1–1,199) 1 (Referent) Tertile 2 (1,200–2,049) 11.4 (3.3–39.6) Tertile 3 (2,050–3,499) 32.4 (6.4–163.9) For both models, a trend test in RR values across cumulative exposure levels (adjusted

Table 2-4. Cholangiocarcinoma (CCA) in Humans Exposed to 1,2-Dichloropropane

Reference and study population	Exposure	Outcomes
		for sex, age, calendar year, and exposure to DCM) was statistically significant (p<0.001)
Occupational reports from print shops in multiple Japanese cities[a]		
Okamoto et al. (2013) Retrospective cohort study (using Japan Health Insurance Association database); 201,937 workers employed in printing and related industries Employment duration: not reported	**Exposure:** No exposure estimates were made; chemicals used in "printing and related industries" not reported	**Cancer effect:** CCA incidence (based on health insurance claims) was 76/201,937 (0.04%) of workers in printing and related industries SPRR (95% CI) for CCA among workers in printing and related industries All: 1.28 (0.91–1.79) Males: 1.31 (0.91–1.89) Males ages 30–49: 1.78 (0.63–5.00)
Kubo et al. 2014b Case-series report of nine male printers diagnosed with CCA between 1988 and 2011 from 11 print shops in Japan (Osaka, Miyagi, Fukuoka, Hokkaido, Aomori, Saitama, Aichi) Employment duration: 3–19 years (mean 13 years)	**Exposure:** Exposure to 1,2-DCP, DCM, and TCE was determined based on job history; reported "high" levels of all three chemicals, but no quantitative exposure estimates were calculated 1,2-DCP (3–16 years exposure) DCM (3–19 years exposure) TCE (duration of exposure not reported) Note: not all cases exposed to all three solvents	**Cancer effect:** Case reports of nine CCA cases in seven print shops (cancer incidence not estimated) Based on job history: 7/9 cases exposed to 1,2-DCP 9/9 cases exposed to DCM 4/9 cases exposed to TCE Note: The two cases without 1,2-DCP exposure were exposed to both DCM and TCE

Table 2-4. Cholangiocarcinoma (CCA) in Humans Exposed to 1,2-Dichloropropane

Reference and study population	Exposure	Outcomes
Yamada et al. 2014 Case-series report of six male printers diagnosed with CCA between 1998 and 2013 from three print shops in Japan (Miyagi, Fukuoka, Hokkaido) Employment duration: 10–16 years	**Exposure:** Exposure levels were not measured; estimates were based on amounts of the chemicals reportedly used 1,2-DCP (ppm): Shop 1: 80–170; Shop 2: 62–200; Shop 3: 110–240 DCM (ppm): Shop 1: <1; Shop 2: 0–180; Shop 3: 0–180 TCE Shops 1 and 3: used (no exposure estimates) DCFE: Shop 2: used (no exposure estimates)	**Cancer effect:** Case reports of six CCA cases in three print shops (cancer incidence not estimated) Based on job history: 6/6 cases exposed to 1,2-DCP 4/6 cases exposed to DCM 4/6 cases exposed to TCE 2/6 cases exposed to DCFE
Yamada et al. 2015a Case-series report of seven male printers diagnosed with CCA between 2002 and 2011 from eight print shops in Japan from five cities (Osaka, Aichi, Shizuoka, Saitama, Aomori); one printer worked in both Shop 2 and 3 Employment duration: 4–19 years	**Exposure:** Exposure levels were not measured; estimates were based on amounts of the chemicals reportedly used 1,2-DCP (shift TWAs in ppm) Shop 1: 92–100; Shop 2: 16–29; Shop 4: 7–17; Shop 5: 58–210; no exposure in Shops 3, 6, 7, 8 DCM (shift TWAs in ppm) Shop 1: 15–18; Shop 2: 25–55; Shop 3: 68–94; Shop 4: 20; Shop 5: 31–270; Shop 6: 84–90; Shop 7: 440; Shop 8: 77–110 TCE Shops 5, 6, and 7: used (no exposure estimates) DCFE: Shop 5: used (no exposure estimates)	**Cancer effect:** Case reports of seven CCA cases in eight print shops (cancer incidence not estimated) Based on job history: 4/7 cases exposed to 1,2-DCP 7/7 cases exposed to DCM 3/7 cases exposed to TCE 1/7 cases exposed to DCFE

Table 2-4. Cholangiocarcinoma (CCA) in Humans Exposed to 1,2-Dichloropropane

Reference and study population	Exposure	Outcomes
Yamada et al. 2015b Case-series report of five male printers and one male coater diagnosed with CCA between 1993 and 2013 from seven print shops and two coating shops in Japan from four cities (Fukuoka, Aichi, Tokyo, Kyoto); one printer worked in Shops 2–4, and the one coater worked in Shops 8+9; there is no case overlap with Yamada et al. (2014) or (2015a) Employment duration: 9–30 years	**Exposure:** Exposure levels were not measured; estimates were based on amounts of the chemicals reportedly used Print shops: 1,2-DCP (shift TWAs in ppm) Shop 1: 74–170; Shop 3: 200; Shop 4: 230; Shop 5: 130–160; Shop 6: 13–65; Shop 7: 59; no exposure in Shop 2 DCM (shift TWAs in ppm) Shop 1: 35–140; Shop 3: 300; Shop 4: 350; Shop 5: 240–470; Shop 6: 20–98; Shop 7: 170–370; no exposure in Shops 2, 8, 9 TCE Shops 6 and 7: used (no exposure estimates) DCFE: Shops 1 and 6: used (no exposure estimates) Coating shops: 1,2-DCP (shift TWAs in ppm): Shop 8: 19; Shop 9: 5 DCFE: Shops 8 and 9: used (no exposure estimates)	**Cancer effect:** Case reports of six CCA cases in seven print shops and two coating shops (cancer incidence not estimated) Based on job history: 6/6 cases exposed to 1,2-DCP 5/6 cases exposed to DCM 2/6 cases exposed to TCE 3/6 cases exposed to DCFE

[a]The cases reported by Okamoto et al. (2013), Kubo et al. (2014a), and Yamada et al. (2014, 2015a, 2015b) are distinct from the 17 cases reported by Kumagai et al. (2013, 2014, 2016), Kubo et al. (2014a), or Sobue et al. (2015). However, it is unclear if there is overlap between the cases reported by Okamoto et al. (2013), Kubo et al. (2014b), or Yamada et al. (2014, 2015a, 2015b).

1,2-DCP = 1,2-dichloropropane; CI = confidence interval; DCFE = 1,1-dichloro-1-fluoroethane; DCM = dichloromethane; JNIOSH = Japanese National Institute of Occupational Safety and Health; RR = relative risk; SIR = standardized incidence ratio; SMR = standardized mortality ratio; SPRR = standardized prevalence rate ratio; TCE = 1,1,1-trichloroethane; TWA = time-weighted average

from 1991 to 2006 in the currently operational shop ranged from 190 to 310 ppm in the printing area and from 70 to 110 ppm in the front room (Kumagai et al. 2013). Between 1991 and 1997/1998, dichloromethane estimated exposure levels ranged from 140 to 360 ppm in the print shop and from 50 to 130 ppm in the front room; 1,1,1-trichloroethane exposure levels from 1991 to 1992 were not estimated (Kumagai et al. 2013). Of the 17 cases, 16 were male printers and 1 was a male front-room worker (Kumagai et al. 2016). The lack of female cases cannot be interpreted due to the low number of female subjects.

Several analyses have been conducted to estimate the potential risk of developing CCA following exposure to chlorinated solvents using employment records from the Japanese printing company described above (Kumagai et al. 2013, 2014; Sobue et al. 2015; see Table 2-4). The most complete analysis combined workers from the four plants that were open continuously including 71 printers (65 males, 6 females) and 24 front room/delivery workers (13 males, 11 females). When considering these four plants together, the CCA incidence was 17/95 (18%), which was significantly elevated compared with the incidence expected based on the rates in the general Japanese population (0.02%), both in workers exposed to 1,2-dichloropropane only or both 1,2-dichloropropane and dichloromethane (Kumagai et al. 2016). Further analysis reported a statistically significant increase in relative risk across cumulative exposure to 1,2-dichloropropane (see Table 2-4). The relative risk of CCA in workers exposed to dichloromethane, compared to those not exposed, was not significantly elevated (Kumagai et al. 2016). Based on this analysis, the study authors concluded that there was a dose-related increased risk of CCA in printers exposed to 1,2-dichloropropane (Kumagai et al. 2016).

Additional case-series reports from Japan have demonstrated that CCA cases in printers are not limited to a single company (see Table 2-4). In a series of papers, Yamada et al. (2014, 2015a, 2015b) identified 19 male printers diagnosed with CCA between 1993 and 2013 from 19 print shops across several Japanese cities. Most printers diagnosed with CCA were exposed to both 1,2-dichloropropane and dichloromethane (13/19) at estimated levels of 5–240 and 15–470 ppm, respectively. Of the remaining six cases, three were exposed to1,2-dichloropropane and three were exposed to dichloromethane. Additional exposures in some cases included unreported levels of 1,1,1-trichloroethane and/or 1,1-dichloro-1-fluorethane. Kubo et al. (2014b) also reported a series of nine cases of CCA diagnosed between 1988 and 2011 in male printers from 11 print shops in seven different Japanese cites; it is not clear if there is any overlap between these cases and the ones reported by Yamada et al. (2014, 2015a, 2015b). Based on work history, these men were exposed to 1,2-dichloropropane (7/9), dichloromethane (9/9), and/or 1,1,1-trichloroethane (4/9); no exposure estimates were calculated. Both cases without 1,2-dichloropropane exposure were exposed to both dichloromethane and 1,1,1-trichloroethane (Kubo et

al. 2014b). Collectively, these case-series reports concluded that occupational exposure to high levels of chlorinated solvents, including 1,2-dichloropropane, may increase the risk of CCA. However, using health insurance claims to the Japan Health Insurance Association, Okamoto et al. (2013) did not find a nationwide excess prevalence of CCA in workers from printing and related industries (n=201, 937), compared with other industries. Chemical exposures were not discussed or estimated in this report, so it is unclear if all workers from printing and related industries were occupationally exposed to chlorinated solvents (Okamoto et al. 2013).

Only two reports evaluated the potential association between CCA and working in printing occupations outside of Japan, neither of which specifically indicated exposure to 1,2-dichloropropane. In Finland, Iceland, Norway, and Sweden, the incidence for intrahepatic CCA was significantly elevated in men employed as "printers or related workers", compared to the general population (standardized incidence ratio [SIR] 2.34, 95% confidence interval [CI] 1.45–3.57), but not female printers or related workers (SIR 1.95, 95% CI 0.84–3.85) (Vlaanderen et al. 2013). The incidence of extrahepatic CCA was not significantly elevated in either male or female printers or related workers (SIRs 1.13 and 0.84, 95% CIs 0.85–1.48 and 0.59–1.19, respectively) (Vlaanderen et al. 2013). In a similar population-based, case-control study conducted in nine unidentified European countries, the risk of extrahepatic CCA was significantly elevated among typesetters, compared with other occupations (odds ratio [OR] 5.78, 95% CI 1.43–23.29), but not printing workers (OR 2.42, 95% CI 0.81–7.24) (Ahrens et al. 2014). While these two reports do not inform regarding the potential association between 1,2-dichloropropane and CCA, they establish that CCA in printers is not exclusive to print shops in Japan or to individuals of Japanese descent.

One study reported a potential association between 1,2-dichloropropane exposure and breast cancer in the general population. In the prospective Sister Study cohort of 49,718 women in the United States, the potential association between air pollutants and breast cancer was examined using census tract air toxic concentration estimates of residential addresses based on the 2005 National Air Toxics Assessment (Niehoff et al. 2019). Mean 1,2-dichloroprane exposure levels were $1.59x10^{-3}$ $\mu g/m^3$ (Quintile 1: $<5.15x10^{-4}$ $\mu g/m^3$; Quintile 5: $>1.93x10^{-3}$ $\mu g/m^3$). No significant increase in risk was found between quintiles of estimated 1,2-dichloropropane exposure and overall rates of breast cancer. However, there was a significant trend toward increased risk of estrogen receptor positive (ER+) invasive breast cancer with increased 1,2-dichloropropane exposure, and the hazard ratio (HR) for ER+ breast cancer in the highest quintile of 1,2-dichloropropane exposure was significantly increased (HR_{Q5} 1.19, 95% CI 01.02–1.38) after adjustment for age, race, education, cigarette smoking, and residence type.

1,2-Dichloropropane is carcinogenic in laboratory animals following both inhalation and oral exposure. There is evidence for respiratory tract cancer following inhalation exposure (nasal tumors in rats, lung tumors in mice) and some evidence for neoplastic lesions in the Harderian gland and spleen in male mice. Following oral exposure, there is equivocal evidence of mammary tumors in female rats and some evidence of liver tumors in male and female mice.

Inhalation Exposure. In rats exposed to 500 ppm 1,2-dichloropropane for 104 weeks (5 days/week, 6 hours/day), a statistically significant increase in the number of nasal papillomas was observed in the nasal cavity of male and female rats (15/50 and 9/50, respectively), compared with zero incidence in controls (Umeda et al. 2010). Incidences at 80 or 200 ppm in males were 2/50 and 4/50, respectively; no papillomas were observed in females at these concentrations. These tumors were observed in the anterior nasal region (levels 1 and 2). Additionally, a rare nasal tumor (esthesioneuroepithelioma) was observed in two male rats at 80 ppm and one male rat at 200 ppm. Due to rarity of this tumor (zero incidence in concurrent and historical controls), these tumors may be attributable to 1,2-dichloropropane exposure. However, due to the nonsignificant association with exposure, the CEL for this study was based on nasal papilloma incidence. 1,2-Dichloropropane was not found to be carcinogenic in other tissues in male or female rats.

In mice exposed to 1,2-dichloropropane for 104 weeks (5 days/week, 6 hours/day), exposure-related neoplastic lesions were observed in the lungs of males and females, and the spleen and Harderian gland of males (Matsumoto et al. 2013). The incidence of bronchioloalveolar adenoma and/or carcinoma was significantly increased in male mice at 32 (18/50) and 200 ppm (18/50), but not 80 ppm (14/50), compared with control (9/50). In female mice, a significant concentration-related trend was observed in the incidence of bronchioloalveolar adenoma and/or carcinoma, with a significant increase at 200 ppm (8/50), compared with control (2/50). A significant increase in the incidence of hemangioma and/or hemangiosarcoma in the spleen was also observed in males at 200 ppm (6/50), compared with control (0/50). The incidence of Harderian gland adenomas was significantly concentration-related in male mice (1/50, 2/50, 3/50, and 6/50 at 0, 32, 80, and 200 ppm, respectively). 1,2-Dichloropropane was not found to be carcinogenic in other tissues in male or female mice.

Heppel et al. (1948) examined the hepatocarcinogenic effects of 1,2-dichloropropane resulting from intermediate-duration exposure (37 exposures to 400 ppm for 4–7 hours/exposure). High mortality occurred throughout the study; only three mice survived all exposures plus a 7-month observation period.

Hepatomas were observed in all three mice that survived. The morphology of the hepatomas was inadequately characterized and the incidence in controls was not reported. Due to high mortality and inadequate reporting, this study was not used as a basis for a CEL in mice after intermediate inhalation exposure.

Oral Exposure. In rats exposed to 1,2-dichloropropane via gavage for 103 weeks (5 days/week), the only exposure-related neoplastic finding was a marginal, but statistically significant, increased incidence of adenocarcinomas of the mammary gland in females at 250 mg/kg/day (NTP 1986). Incidences in control, 125, and 250 mg/kg/day females were 1/50, 2/50, and 5/50, respectively. NTP (1986) considered this to be equivocal evidence for carcinogenicity. In support, mammary gland hyperplasia was also significantly elevated in female rats at 125 mg/kg/day. 1,2-Dichloropropane was not found to be carcinogenic in other tissues in the females or in any tissues in male rats (the highest dose tested was 125 mg/kg/day).

In mice exposed via gavage for 103 weeks (5 days/week), exposure-related neoplastic lesions were observed in the liver in males and females, and the thyroid in females (NTP 1986). A significant dose-related increase in liver adenomas was observed in both male and female mice. After adjustment for intercurrent mortality, the incidences in males and females administered 250 mg/kg/day (45.5 and 19.25%, respectively) were significantly increased compared with male and female controls (20 and 2.9%, respectively). Similarly, the incidences of hepatocellular adenoma or carcinoma (combined) were significantly increased in a dose-related manner, with significantly increased incidence at 250 mg/kg/day in males (74.7%), and at 125 and 250 mg/kg/day in females (26.4 and 30.8%, respectively) compared with male and female controls (46.7 and 5.7%, respectively). The incidences of hepatocellular carcinoma alone were not significantly increased in a dose-related manner. A significant increase in thyroid follicular cell adenoma or carcinoma (combined) was also observed in females at 250 mg/kg/day (20.8%), compared with controls (2%), after adjustment for intercurrent mortality. NTP (1986) concluded that there was some evidence for carcinogenicity in male and female mice based on the increased incidences of hepatocellular neoplasms, primarily adenomas.

Gi et al. (2015b) evaluated the potential for 1,2-dichloropropane to promote N-nitrosobis-(2-oxopropyl)amine (BOP)-induced preneoplastic and neoplastic lesions in the liver (including cholangioma), pancreas, lungs, or kidneys in hamsters. Exposure to 1,2-dichloropropane at gavage doses of 62.5 or 125 mg/kg/day for 15–17 weeks (5 days/week) after BOP-initiation (four injections over 7 days) did not promote BOP-induced pre-neoplastic or neoplastic lesions in any tissue examined.

1,2-Dichloropropane also did not increase the incidence of pre-neoplastic or neoplastic lesions in saline-initiated controls.

IARC (2017) concluded that 1,2-dichloropropane is carcinogenic to humans (Group 1) based on evidence that 1,2-dichloropropane exposure causes cancer of the biliary tract (CCA) in occupationally exposed workers and supporting mechanistic data. The EPA PPRTV program determined that 1,2-dichloro-propane is likely to be carcinogenic to humans based on evidence of a potential correlation between occupational exposure to 1,2-dichloropropane and CCA cancer and adequate evidence in laboratory animals (EPA 2016a). The NTP Report on Carcinogens (NTP 2016) has not classified the potential for 1,2-dichloropropane to cause cancer in humans.

Mechanisms of Cancer. The carcinogenic mode of action for 1,2-dichloroprone is not yet fully elucidated (reviewed by Kubo et al. 2018). The available evidence suggests that 1,2-dichloropropane is not a potent mutagen, but it can cause deoxyribonucleic acid (DNA) and chromosomal damage under certain conditions (see Section 2.20, Genotoxicity). Examination of pathological characteristics in 16 printers with CCA associated with 1,2-dichloropropane and/or dichloromethane exposure showed a progression from chronic bile duct injury with DNA damage in large bile ducts, to precursor lesions (biliary intraepithelial neoplasia [BiIIN] and/or intraductal papillary neoplasm of the bile duct [IPNB]), followed by invasive carcinoma (Kinoshita et al. 2016). Specifically, immunohistochemical analysis of surgically resected specimens of CCA cases associated with 1,2-dichloropropane and/or dichloromethane exposure showed increased DNA double-strand breaks in precursor lesions (BiIIN and/or IPNB) compared with CCA cases associated with other causes (e.g., hepatolithiasis) (Sato et al. 2014). Sato et al. (2014) proposed that direct DNA damage caused by glutathione-conjugated reactive metabolites as a contributing factor to the pathogenesis of CCA in humans occupationally exposed to 1,2-dichloropropane (and/or dichloromethane), as studies of bile duct, peribiliary gland, and gallbladder tissue from humans indicates expression of GST T1-1 but low or no expression of CYP2E1. Similar expression patterns were also observed in rats and mice (Sato et al. 2014), and biliary excretion of glutathione conjugated metabolites of 1,2-dichloropropane was observed in rodent species following oral administration (Toyoda et al. 2016). Additional studies in transgenic mouse strains indicate that metabolites are excreted into the bile via the bile canalicular membrane transporter ABCC2 (Toyoda et al. 2016).

An *in vitro* study was conducted to evaluate potential differences in GSH conjugation of 1,2-dichloro propane and dichloromethane, which have both been implicated in the development of occupational CCA (Toyoda et al. 2017). This study showed that 1,2-dichloropropane spontaneously conjugates with GSH

under physiological conditions, while dichloromethane shows very little spontaneous activity. However, GST T1-1 greatly enhanced GSH conjugation with dichloromethane, and only had a mild effect on GSH conjugation with 1,2-dichloropropane. Therefore, while both 1,2-dichloropropane and dichloromethane produce glutathione-conjugated reactive metabolites, there are differences in the metabolic activation processes.

In four cases of occupational CCA, Mimaki et al. (2016) identified a characteristic trinucleotide mutational signature using whole genome analysis, showing strand bias in C:G to T:A mutations. Mimaki et al. (2016) suggested that 1,2-dichloropropane exposure results in DNA adducts on G residues, with mutations occurring during repair processes. Mimaki et al. (2016) further suggested that there may be a distinct mutational signature associated with occupational CCA, which was partially reproduced in *Salmonella typhimurium* bacteria; however, it was not reproduced in human epithelial cells. The potential roles of the DNA editing enzyme activation-induced cytidine deaminase (AID), one of the induced proteins in the transformed epithelial cells in occupational cases of CCA identified by Mimaki et al. (2016), was evaluated in an *in vitro* study in human cholangiocytes (Zong et al. 2019). No changes in AID levels in human cholangiocytes were observed following exposure to 1,2-dichloropropane at concentrations associated with DNA damage; however, when human cholangiocytes were co-incubated with human macrophages, AID protein levels were increased in exposed cholangiocytes and DNA damage was enhanced. The study authors proposed that inflammatory responses in the macrophages mediated via the NF-κB pathway contributed to increased AID induction and DNA damage in cholangiocytes. Support for this mechanism included induction of TNF-α in exposed macrophages; induction of AID, NF-κB, and IκB in cholangiocytes exposed to TNF-α; and decreased induction of TNF-α and AID when cells were co-cultured with SN50, a NF-κB inhibitor.

2.20 GENOTOXICITY

Available evidence indicates that 1,2-dichloropropane is not a potent mutagen. However, there is evidence that it directly interacts with DNA, and is capable of causing DNA damage and chromosomal alterations under certain conditions. Results of *in vitro* and *in vivo* genetic testing of 1,2-dichloropropane are presented in Tables 2-5 and 2-6, respectively, and are summarized below.

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

Species (test system)	Endpoint	Results		Reference
		With activation	Without activation	
Genotoxicity studies in prokaryotic organisms				
Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, TA1538	Gene mutation	+ (TA100, TA1535) – (TA98, TA1537, TA1538)	+ (TA100, TA1535) – (TA98, TA1537, TA1538)	Principe et al. 1981
S. typhimurium strains TA100, TA1535, TA1978	Gene mutation	+	+	De Lorenzo et al. 1977
S. typhimurium strain TA100	Gene mutation	NT	+	Akiba et al. 2017; Mimaki et al. 2016
S. typhimurium strain TA100	Gene mutation	–	–	Stolzenberg and Hine 1980
S. typhimurium strains TA98, TA100, TA1535, TA1537	Gene mutation	–[a]	–[a]	Haworth et al. 1983; Prival and Dunkel 1989
S. typhimurium strains TA98, TA100, TA1535, TA1537	Gene mutation	–	–	NTP 1986; Tennant et al. 1987; Zeiger 1987
S. typhimurium strains TA98, TA100, TA1535, TA1537, TA1538	Gene mutation	–	–	SRI 1975
S. typhimurium strain TA100-GSTT1[b]	Gene mutation	NT	+	Akiba et al. 2017
Streptomyces coelicolor A3	Gene mutation	NT	–	Principe et al. 1981
S. typhimurium TA1535/pSK1002	DNA repair	–	–	Yasunaga et al. 2004
Escherichia coli PQ37	DNA repair	–	–	von der Hude et al. 1988
Genotoxicity studies in nonmammalian eukaryotic organisms				
Aspergillus nidulans	Gene mutation	NT	+	Principe et al. 1981
A. nidulans	Mitotic recombination	NT	–	Crebelli et al. 1984
Saccharomyces cerevisiae D3	Mitotic recombination	–	–	SRI 1975
Genotoxicity studies in mammalian cells				
Human lymphocytes	Unscheduled DNA synthesis	–	–	Perocco et al. 1983
Human hepatocytes	DNA damage	–	+	Toyooka et al. 2017
Human cholangiocytes	DNA damage	–	+	Toyooka et al. 2017
Human cholangiocytes	DNA damage	NT	+	Zong et al. 2019
Mouse lymphoma cells	Gene mutation	+	+	Tennant et al. 1987

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

Species (test system)	Endpoint	Results		Reference
		With activation	Without activation	
Mouse lymphoma cells	Gene mutation	–	+	Myhr and Caspary 1991
Chinese hamster ovary cells	Gene mutation	–	–	Myhr et al. 1988
Chinese hamster ovary cells	Chromosomal aberrations	+	+	Galloway et al. 1987; NTP 1986; Tennant et al. 1987
Chinese hamster ovary cells	Sister chromatid exchanges	+	+	Galloway et al. 1987; NTP 1986; Tennant et al. 1987
Chinese hamster ovary cells	Sister chromatid exchanges	–	+	von der Hude et al. 1987

[a]Marginal (<2-fold increase) results were reported positive by Haworth et al. (1983); however, upon re-evaluation using more stringent criteria (>2-fold induction at concentrations ≤500 µg/plate), Prival and Dunkel (1989) reclassified results as negative
[b]*S. typhimurium* strain expressing human GSTT1.

+ = positive results; – = negative results; DNA = deoxyribonucleic acid; NT = not tested

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

Species (exposure route)	Endpoint	Results	Reference
Human (occupational)	DNA damage (S100P- and γH2AX-postive cells) in invasive carcinoma and precursor lesions (BiIIN and IPNB) from human CCA cases in print shop workers (n=3)	+	Kinoshita et al. 2016
Human (occupational)	DNA damage in cells from precursor lesions (BiIIN and IPNB) from human CCA cases in print shop workers (n=8) or associated with hepatolithiasis (n=16)	+ (7/8 print shop workers; 6/19 hepato-lithiasis cases)	Sato et al. 2014
Rat (oral)	Dominant lethal mutations	–	Hanley et al. 1989
Mouse (inhalation)	*Pig*-a-gene mutations in RBCs	–	Suzuki et al. 2014
Mouse (inhalation)	*gpt* mutations in liver	–	Suzuki et al. 2014
Mouse (inhalation)	Micronuclei in reticulocytes and RBCs	–	Suzuki et al. 2014
Mouse (inhalation)	DNA damage in liver	+	Suzuki et al. 2014
Mouse (inhalation)	DNA damage in liver	+	Toyooka et al. 2017
Mouse (oral)	Oxidative DNA damage in liver	–	Gi et al. 2015a
Hamster (oral)	Oxidative DNA damage in liver	–	Gi et al. 2015a
Drosophila melanogaster (inhalation)	Mitotic recombination (wing spot assay)	+	Chroust et al. 2007

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

Species (exposure route)	Endpoint	Results	Reference
D. melanogaster (inhalation)	Sex-linked recessive lethal mutations	–	Kramers et al. 1991
D. melanogaster (inhalation)	Sex-linked recessive lethal mutations	–	Woodruff et al. 1985
D. melanogaster (injection)	Sex-linked recessive lethal mutations	–	Woodruff et al. 1985

– = negative result; + = positive result; BiIIN = biliary intraepithelial neoplasia; DNA = deoxyribonucleic acid; IPNB = intraductal papillary neoplasm of the bile duct; RBC = red blood cell

Mutagenicity. High concentrations of 1,2-dichloropropane (≥750 µg/plate) were reported as mutagenic in various strains of *S. typhimurium* with or without metabolic activation in some early assays (De Lorenzo et al. 1977; Haworth et al. 1983; Principe et al. 1981). More stringent criteria established in the mid-1980s, requiring >2-fold induction at concentrations of <500 µg/plate, resulted in a lack of significant mutagenicity in the Haworth et al. (1983) study (Prival and Dunkel 1989). Other evaluations determined that 1,2-dichloropropane was not mutagenic to *S. typhimurium* or *Streptomyces coelicolor* with or without metabolic activation. (NTP 1986; Principe et al. 1981; SRI 1975; Stolzenberg and Hine 1980; Tennant et al. 1987; Zeiger 1987). However, dose-dependent mutagenicity was reported in *S. typhimurium* strain TA100 at vapor concentrations ranging from 600 to 4,000 ppm without metabolic activation using a closed plate system (Akiba et al. 2017; Mimaki et al. 2016); Mimaki et al. (2016) did not report cell survival, but Akiba et al. (2017) reported no cytotoxicity at concentrations up to 3,000 ppm. Akiba et al. (2017) also reported dose-dependent mutagenicity in an *S. typhimurium* strain TA100 that expressed human GSTT1 at vapor concentrations ranging from 600 to 3,000 ppm without metabolic activation using a closed system; no cytotoxicity was observed, and mutagenic potential was similar to the standard TA100 strain. In one study, 1,2-dichloropropane induced gene mutations in *Aspergillus nidulans* (Principe et al. 1981). In mammalian cells, Tennant et al. (1987) reported gene mutation in mouse lymphoma cells with or without metabolic activation, while Myhr and Caspary (1991) only observed mutations in mouse lymphoma cells without activation. In *in vivo* studies, 1,2-dichloro-propane did not induce sex-linked recessive lethal mutations in *Drosophila melanogaster* exposed via injection or inhalation for up to 2 weeks (Kramers et al. 1991; Woodruff et al. 1985), dominant lethal mutations in rats exposed to doses up to 162 mg/kg/day via drinking water for 14 weeks (Hanley et al. 1989), *gpt* mutations in mouse liver following exposure to 300 ppm via inhalation for 4 weeks (Suzuki et al. 2014), or *Pig*-a-gene mutations in mouse erythrocytes following exposure to concentrations up to 600 ppm via inhalation for 6 weeks (Suzuki et al. 2014).

Clastogenicity. Chromosomal aberrations and sister chromatid exchanges were induced in Chinese hamster ovary cells with and without metabolic activation (Galloway et al. 1987; NTP 1986; Tennant et al. 1987; von der Hude et al. 1987). Mitotic recombination was not observed in *A. nidulans* or *Saccharomyces cerevisiae* (Crebelli et al. 1984; SRI 1975). Data from *in vivo* studies show that 1,2-dichloropropane does not induce micronuclei in mouse reticulocytes or erythrocytes following inhalation exposure (Suzuki et al. 2014). Additionally, 1,2-dichloropropane induced mitotic recombination in *D. melanogaster* (Chroust et al. 2007).

DNA Damage. Sato et al. (2014) reported that double-stranded DNA breaks were observed in precursor lesions associated with CCA (BiIIN and IPNB) more than twice as often in cases attributed to 1,2-dichloropropane and/or dichloromethane exposure in Japanese print shops compared with cases associated with hepatolithiasis or conventional IPNB. Double-stranded DNA breaks in IPNB lesions were observed in 7/8 cases associated with occupational exposure to 1,2-dichloropropane and/or dichloromethane (88%), 7/16 cases associated with hepatolithiasis (44%), and 6/19 cases of conventional IPNB (32%). Similarly, double-stranded DNA breaks in BiIIN lesions were observed in 6/8 cases associated with occupational exposure to 1,2-dichloropropane and/or dichloromethane (75%) and 3/16 cases associated with hepatolithiasis (19%). Using immunohistochemical markers of DNA damage (S100P and γH2AX), Kinoshita et al. (2016) reported DNA damage localized to invasive carcinoma and precursor lesions (BiIIN and IPNB) in the bile ducts of Japanese printers with CCA attributed to 1,2-dichloropropane and/or dichloromethane exposure; γH2AX-positive cells were also observed in non-neoplastic biliary epithelium (no S100-P positive cells). In laboratory animals, DNA damage was also observed in the livers of mice following acute- or intermediate-duration inhalation exposure to concentrations ≥100 ppm (Suzuki et al. 2014; Toyooka et al. 2017). Observed damage is likely due to direct interaction with DNA, as levels of 8-OHdG (a marker of oxidative DNA damage) were not elevated in the livers of mice or hamsters following exposure to gavage doses up to 250 mg/kg/day for 4 weeks (Gi et al. 2015a).

1,2-Dichloropropane did not induce DNA repair in bacterial systems (von der Hude et al. 1988; Yasunaga et al. 2004) or unscheduled DNA synthesis in cultured human lymphocytes (Perocco et al. 1983). However, DNA damage was observed in cultured human hepatocytes and cholangiocytes exposed to 1,2-dichloropropane (Toyooka et al. 2017; Zong et al. 2019). Observed DNA damage was enhanced in cholangiocytes when they were cocultured with human macrophages; the study authors attributed this to proinflammatory signaling from the exposed macrophages (Zong et al. 2019).

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

3.1 TOXICOKINETICS

No studies were located regarding 1,2-dichloropropane toxicokinetics in humans. Data from animal studies are summarized below.

- 1,2-Dichloropropane is rapidly and extensively absorbed following inhalation and oral exposure. The rate and extent of dermal absorption is unknown.
- 1,2-Dichloropropane appears to be widely distributed throughout the body following inhalation and oral exposure. For both exposure routes, the highest levels were found in the liver, kidney, and blood; high levels were also observed in the lung following inhalation exposure. The distribution following dermal exposure is unknown.
- The predominant pathway for 1,2-dichloropropane metabolism consists of oxidation of the C-position of the parent compound followed by glutathione conjugation resulting in formation of mercapturic acids (N-acetyl-S-(2-hydroxypropyl)-L-cysteine, N-acetyl-S-(2-oxopropyl)-L-cysteine, and N-acetyl-S-(l-carboxyethyl)-L-cysteine). 1,2-Dichloropropane may also conjugate with lactate, forming carbon dioxide and acetyl Co-A.
- The primary routes of excretion following oral, inhalation, or intraperitoneal exposure are urine and expired air, with small amounts excreted in feces following oral exposure.

3.1.1 Absorption

No studies were located regarding the rate and extent of absorption of 1,2-dichloropropane following inhalation exposure in humans. Available data from rats indicate that 1,2-dichloropropane is rapidly and extensively absorbed following inhalation exposure (Take et al. 2014; Timchalk et al. 1989, 1991). During a 3-hour exposure to 80 or 500 ppm, blood concentrations in rats rapidly increased within the first 60 minutes, with concentrations in blood being dictated by the blood-to-gas partition coefficient (Take et al. 2014). During the first 24 hours after a 6-hour exposure of rats to ^{14}C-1,2-dichloropropane (5, 50, or 100 ppm), 71–88% of the recovered dose was found in the excreta, with 55–65% of the recovered dose found in the urine, and 16–23% of the recovered dose found in expired air as $^{14}CO_2$ (Timchalk et al. 1989, 1991). These data suggest that 1,2-dichloropropane was absorbed through the lungs. The data indicate that 1,2-dichloropropane was rapidly absorbed according to a zero-order input, but that absorption was not linear with respect to the concentration of 1,2-dichloropropane. The authors assumed that 60% of the inspired concentration of ^{14}C-1,2-dichloropropane was absorbed, but the basis for this assumption was not reported (Timchalk et al. 1989). Gargas et al. (1989) reported blood:air partition coefficients for humans

and rats of 8.75±0.50 and 18.7±0.5, respectively, indicating that 1,2-dichloropropane is readily absorbed from the lungs.

No studies were located regarding the rate and extent of absorption of 1,2-dichloropropane following oral exposure in humans. Take et al. (2017) reported peak blood concentrations of 1,2-dichloropropane in rats 1–3 hours after oral exposure. Other studies in rats by Hutson et al. (1971) and Timchalk et al. (1989, 1991), which found that an average of 74–95% of the ^{14}C-labeled 1,2-dichloropropane dose was excreted in the urine or in expired air within 24 hours of dosing, suggest that 1,2-dichloropropane is readily and extensively absorbed from the gastrointestinal tract. This is supported by the fact that only 0.5% of the administered dose remained in the gut 4 days after administration (Hutson et al. 1971).

No studies were located regarding the rate and extent of absorption of 1,2-dichloropropane following dermal exposure in humans or animals. It can be inferred that 1,2-dichloropropane is absorbed by the skin based on studies reporting lethality in rabbits following dermal exposure (see Section 2.1). Systemic toxicity (acute renal failure, impaired liver function, acute hepatocellular necrosis, rhabdomyolysis, and severe disseminated intravascular coagulation) in a human case report following prolonged dermal exposure (~5 hours) to a commercial fixative containing 30–40% 1,2-dichloropropane and 33–38% toluene (Fiaccadori et al. 2003) may also be attributable to dermal absorption of 1,2-dichloropropane and/or toluene. A human skin permeability constant of 0.01 cm/hour and a permeability coefficient of 0.206 cm/hour were calculated by EPA (1992). Additionally, Fiserova-Bergerova et al. (1990) estimated that 1,2-dichloropropane had a significant dermal absorption potential based on a dermal penetration rate (flux) predicted from physical properties.

3.1.2 Distribution

No studies were located regarding the distribution of 1,2-dichloropropane following inhalation exposure in humans. After rats were exposed for 6 hours to 5, 50, or 100 ppm ^{14}C-labeled 1,2-dichloropropane, the radioactivity was well distributed among the major tissues, with the highest concentration in the liver, kidneys, lungs, and blood (Timchalk et al. 1989, 1991). Similarly, rats exposed to 80 or 500 ppm for 3 hours showed widespread distribution; however, the highest concentration was observed in abdominal fat (Take et al. 2014).

No studies were located regarding the distribution of 1,2-dichloropropane following oral exposure in humans. Following oral administration of 100 mg/kg ^{14}C-labeled 1,2-dichloropropane, Timchalk et al.

(1989, 1991) observed that radioactivity was well distributed among the major tissues at 48 hours in rats. The distribution of radioactivity in the tissues of rats was similar following inhalation and oral exposure to 1,2-dichloropropane in the Timchalk et al. (1989, 1991) study, with the exception of the lungs (low radioactivity after oral exposure). Take et al. (2017) evaluated distribution of ^{14}C-labeled 1,2-dichloropropane in blood, abdominal fat, lungs, liver, and kidneys following oral exposure to 62 or 125 mg/kg in rats and reported a higher concentration in abdominal fat compared to blood and other tissues at both doses. Twenty-four hours after exposure, 1,2- dichloropropane was only detectible in blood and abdominal fat of rats given 62 mg/kg, and was detected in the blood, liver, kidneys, lungs, and abdominal fat of rats given 125 mg/kg. These findings suggest that low levels of 1,2- dichloropropane can remain in tissues for prolonged periods after exposure. In support, 1.5 and 3.5% of the ^{14}C dose were found in the skin and carcass, respectively, in rats 96-hours after exposure to 4.8 mg/kg ^{14}C-labeled 1,2-dichloropropane (Hutson et al. 1971).

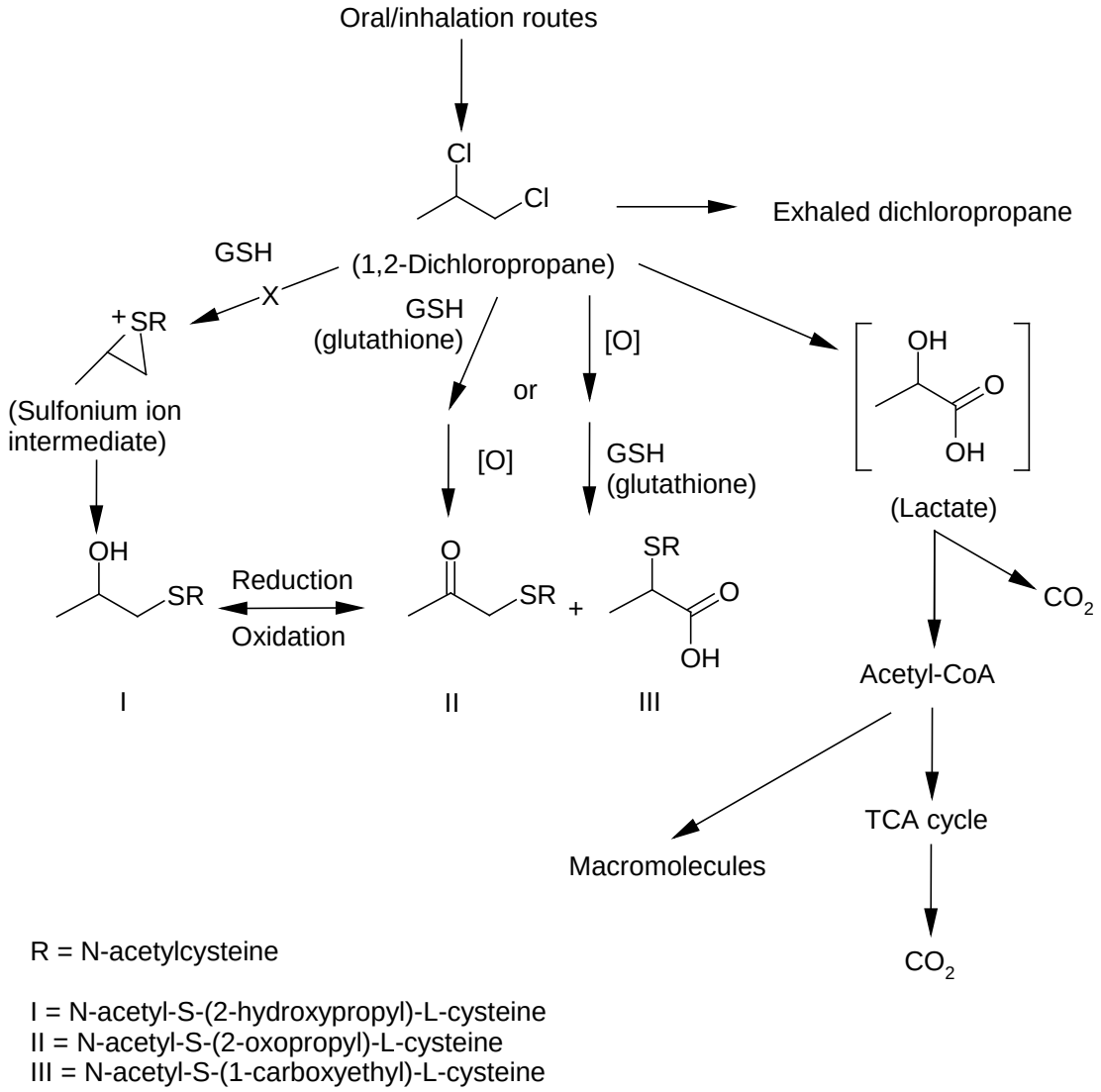
No studies were located regarding the distribution of 1,2-dichloropropane following dermal exposure in humans or animals.

3.1.3 Metabolism

No studies were located regarding the metabolism of 1,2-dichloropropane in humans. The proposed metabolic pathways for 1,2-dichloropropane, based on data from rat studies, are shown in Figure 3-1. The primary pathway consists of oxidation of the C-position of the parent compound by CYP2E1 followed by glutathione conjugation by glutathione S-transferase (GST) T1-1 (Bartels and Timchalk 1990; Gi et al. 2015a; Gonzalez and Gelboin 1994; Guengerich et al. 1991; Sato et al. 2014; Yanagiba et al. 2016). The major urinary metabolites in rats resulting from this metabolic pathway include three mercapturic acids: N-acetyl-S-(2-hydroxypropyl)-L-cysteine, N-acetyl-S-(2-oxopropyl)-L-cysteine, and N-acetyl-S-(l-carboxyethyl)-L-cysteine (Bartels and Timchalk 1990; Jones and Gibson 1980; Timchalk et al. 1989, 1991; Trevisan et al. 1988). These metabolites accounted for approximately 84% of the urinary metabolites excreted following exposure (Timchalk et al. 1989, 1991). Additional minor metabolites identified in urine include N-acetyl-S-(2,3-dihydroxypropl)cysteine, β-chlorolactaldehyde, and β-chlorolactate (Jones and Gibson 1980). 1,2-Dichloropropane may also conjugate with lactate, forming carbon dioxide and acetyl Co-A. Acetyl Co-A may then enter the tricarboxylic acid cycle and generate more carbon dioxide or may be utilized in various biosynthetic pathways (Timchalk et al. 1989, 1991). Hutson et al. (1971) administered 4.8 mg/kg ^{14}C-labeled 1,2-dichloropropane orally to rats, and 42.4% of

the given dose was measured in the expired air after 96 hours. Of the 42.4%, 19.3% was expired as ^{14}C-labeled carbon dioxide, indicating that extensive metabolism of 1,2-dichloropropane had occurred.

Figure 3-1. Proposed Metabolic Scheme for 1,2-Dichloropropane in the Rat (R = N-Acetylcysteine)



3.1.4 Excretion

Data on excretion of 1,2-dichloropropane are limited to a biomarker study that reports a correlation between occupational 1,2-dichloropropane air levels and unmetabolized 1,2-dichloropropane levels in end-of-shift urine samples from exposed workers (Kawai et al. 2015). This indicates that urine is a route

of excretion in humans following inhalation exposure. No additional studies were located regarding the rate or route of excretion of 1,2-dichloropropane following exposure in humans.

In animals, the primary routes of excretion following oral, inhalation, or intraperitoneal exposure are urine and expired air, with small amounts excreted in feces following oral exposure (Hutson et al. 1971; Jones and Gibson 1980; Timchalk et al. 1989, 1991; Trevisan et al. 1988). Toyoda et al. (2016) showed that glutathione-conjugated metabolites of 1,2-dichloropropane are also excreted into the bile via the bile canalicular membrane transporter ABCC2 following exposure to high oral doses (500 mg/kg). With inhalation exposure, the relative contribution of excretion via expired air increased with increased exposure levels (Timchalk et al. 1989, 1991). For example, in rats exposed to 5, 50, or 100 ppm of ^{14}C-labeled 1,2-dichloropropane vapors for 6 hours, the principal routes of elimination were the urine and expired air; 55–65% of the recovered dose was excreted in the urine, expired carbon dioxide accounted for 16–23% of the recovered dose, and 1.7, 2.1–3.4, and 6–7% of the recovered dose was expired as organic volatiles in the 5, 50, and 100 ppm groups, respectively (Timchalk et al. 1989, 1991). The majority of the administered dose was excreted within the first 24 hours after exposure. Similarly, 80–90% of the administered dose was excreted in the urine, feces, and expired air within 24 hours in rats that were administered one dose of 4.0 mg/kg ^{14}C-labeled 1,2-dichloropropane by gavage (Hutson et al. 1971). After 24 hours, males had excreted 48.5% of the dose in the urine and 5.0% of the dose in the feces. Females had excreted 51.9% of the dose in the urine and 3.8% of the dose in the feces in the same time period. Therefore, the percentage of radioactivity in expired air after 24 hours ranged from 24.3 to 36.5% of the dose in both sexes. In a separate experiment, 42.4% of the administered ^{14}C dose of 4.8 mg/kg ^{14}C-labeled 1,2-dichloropropane was detected in the expired air after 96 hours (Hutson et al. 1971). Similar results were observed in rats administered 1 or 100 mg/kg of ^{14}C-labeled 1,2-dichloropropane (Timchalk et al. 1989, 1991). Elimination patterns were similar with single and repeat oral exposures, suggesting that accumulation of 1,2-dichloropropane in the body is not expected.

Elimination half-life ($t_{1/2}$) values and area under the curve values over the first 1,440 minutes ($AUC_{0–1,440}$) were estimated in rats for blood and select organs following inhalation or oral exposure (Take et al. 2014, 2017). Values are presented in Tables 3-1 and 3-2, respectively. These values support that at low levels, accumulation of 1,2-dichloropropane in the body is not expected; however, concentration in body fat is predicted if the metabolic capacity is exceeded following high-level inhalation or oral exposures.

Table 3-1. Elimination Half-Lives ($t_{1/2}$) and $AUC_{0–1,440}$ in Rats for 1,2-Dichloropropane Following a 3-Hour Inhalation Exposure

Tissue	Exposure level (ppm)	Elimination $t_{1/2}$ (minutes)	$AUC_{0–1,440}$ (µg/mL in blood, µg/g in tissue)
Blood	80	182	251
	500	168	3,272
Lung	80	39	122
	500	61	2,352
Liver	80	57	425
	500	125	7,113
Kidney	80	59	317
	500	127	4,951
Abdominal fat	80	154	9,553
	500	186	139,711

$AUC_{0–1,440}$ = area under the curve values over the first 1,440 minutes

Source: Take et al. 2014

Table 3-2. Elimination Half-Lives ($t_{1/2}$) and $AUC_{0\text{-}1,440}$ in Rats for 1,2-Dichloropropane Following a Single Gavage Exposure

Tissue	Dose (mg/kg)	Elimination $t_{1/2}$ (minutes)	$AUC_{0\text{-}1440}$ (µg/mL in blood, µg/g in tissue)
Blood	62	193	359
	125	315	992
Lung	62	144	2,038
	125	187	6,436
Liver	62	144	1,034
	125	193	3,125
Kidney	62	114	527
	125	165	1,867
Abdominal fat	62	257	17,771
	125	330	49,731

$AUC_{0–1,440}$ = area under the curve values over the first 1,440 minutes

Source: Take et al. 2017

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.

No chemical specific PBPK models have been developed. However, Timchalk et al. (1989, 1991) described the time course of 1,2-dichloropropane in the blood as a one-compartment open pharmacokinetic model, with zero-order input and first-order elimination. In rats exposed to 50 or 100 ppm 1,2-dichloropropane vapors for 6 hours, the peak blood concentrations were 17–19- and 68–84-fold higher, respectively, than the peak blood concentration of the 5-ppm group. This dose-dependent nonlinearity of blood clearance suggests that metabolism and/or elimination of 1,2-dichloropropane becomes saturated with increasing concentrations (Timchalk et al. 1989).

3.1.6 Animal-to-Human Extrapolations

No studies were identified that could evaluate potential differences in the toxicity or toxicokinetics of 1,2-dichloropropane between humans and animals. In the absence of adequate human toxicokinetic studies, animal data are assumed relevant to humans. In addition, most primary toxicity targets identified in animal studies (respiratory, hepatic, hematological, neurological) have been reported in case studies of humans following exposure to high levels of 1,2-dichloropropane. Some species differences were observed between different laboratory species; however, the targets of toxicity appear to be similar. Available mechanistic data are inadequate to evaluate potential species differences.

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

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

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these

chemicals in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

Populations at greater exposure risk to unusually high exposure levels to 1,2-dichloropropane are discussed in Section 5.7, Populations with Potentially High Exposures.

No populations with unusual or increased susceptibility to the health effects of 1,2-dichloropropane were identified based on the available literature. It is unclear if the developing fetus or neonate are uniquely susceptible to toxic effects of 1,2-dichloropropane, as all available studies report developmental effects at doses associated with parental toxicity (Kirk et al. 1990, 1995). Based on glutathione conjugation during metabolism of 1,2-dichloropropane (see Section 3.1.3), differences in glutathione metabolism due to life-stage and/or genotype may alter susceptibility. For example, individuals with GSTM1- and GSTT1-positive genotypes have full reduced glutathione conjugating capability, which may result in more efficient production of toxic derivatives (Fiaccadori et al. 2003). In addition, differential expression of GST isoforms has been reported during developmental stages, compared to adults, which may alter the glutathione conjugating rate and capability (Raijmakers et al. 2001). Similar differences in hepatic cytochrome P450 expression have been reported throughout development (Hines 2007). These potential differences in age-related metabolism may infer differential susceptibility in the developing fetus, neonate, or child.

Due to the potential role of glutathione depletion in the toxicity of 1,2-dichloropropane (see Sections 2.7, 2.9, and 2.10), individuals with inherited glucose-6-phosphate dehydrogenase (G6PDH) deficiency may be more susceptible to toxicity. The biological implications of genetic G6PDH deficiency, an x-linked inherited disorder most commonly found in individuals of African, Asian, Mediterranean, or Middle Eastern descent, are well established and extensively reviewed (e.g., Cappellini and Fiorelli 2008; Frank 2005; Harcke et al. 2019). G6PDH deficiency decreases the ability to reduce oxidized glutathione due to reduced capacity to produce nicotinamide adenine dinucleotide phosphate (NADPH) via the pentose phosphate pathway. This results in increased glutathione depletion following both intrinsic and extrinsic sources of oxidative stress in individuals with genetic G6PDH deficiency, compared to the general population. Since NADPH in erythrocytes is only formed via the pentose phosphate pathway (due to lack of mitochondria), individuals with genetic G6PDH deficiency are particularly vulnerable to chemical-induced hemolytic anemia. No studies specifically evaluating susceptibility to 1,2-dichloropropane toxicity in individuals with G6PDH deficiency were identified; however, individuals with genetic G6PDH

variants are known to have increased susceptibility to naphthalene- and 2,4,6-trinitrotoluene-induced hemolytic anemia (Harcke et al. 2019; Santucci and Shah 2000). Based on the known impairments associated with genetic G6PDH deficiency, evidence of glutathione depletion following exposure to 1,2-dichloropropane, and supporting data from chemicals with the same proposed mechanism of action, individuals with genetic G6PDH deficiency may be more susceptible to 1,2-dichloropropane toxicity, particularly hemolytic anemia.

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 1,2-dichloropropane are discussed in Section 3.3.1. The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see http://www.cdc.gov/exposurereport/). If available, biomonitoring data for 1,2-dichloropropane from this report are discussed in Section 5.6, General Population Exposure.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that (depending on magnitude) can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effect caused by 1,2-dichloropropane 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

Unmetabolized parent compound levels in the urine have been proposed as a reliable biomarker of exposure for organic solvents, including 1,2-dichloropropane (Ghittori et al. 1987; Kawai et al. 2015). Kawai et al. (2015) showed significant correlation of 1,2-dichloropropane levels in workplace air with 1,2-dichloropropane levels in end-of-shift urine samples in print shop workers. Ghittori et al. (1987) calculated that a urinary concentration of 1,2-dichloropropane of 268 µg/L is equivalent to an air exposure concentration of 300 µg/L. Detection of metabolites in the urine could also be considered as a biomarker of exposure; however, Kawai et al. (2015) indicated that tests for unmetabolized 1,2-dichloropropane are more straightforward.

Unmetabolized 1,2-dichloropropane in whole blood was used in the National Health and Nutritional Examination Survey (NHANES) as a biomarker to generate data on general U.S. population exposures between 2002 and 2012 (CDC 2019). In all years evaluated, blood levels were below the level of detection using this analytical method (0.008 µg/L; see details in Section 5.6). While background levels in the general population appear to be below the level of detection of this analytical method, Kirman et al. (2012) and Aylward et al. (2010) indicate that the whole blood analytical method used to collect NHANES data is sensitive enough to detect recent toxicologically relevant exposures.

Glutathione conjugated metabolites in the serum have also been proposed as biomarkers of exposure based on studies in rats (Toyoda et al. 2016).

3.3.2 Biomarkers of Effect

There are no specific biomarkers used to characterize the effects from 1,2-dichloropropane exposure, as biomarkers of effects for 1,2-dichloropropane are likely to be common to the general class of chlorinated solvents, rather than specific for 1,2-dichloropropane.

3.4 INTERACTIONS WITH OTHER CHEMICALS

Based on epidemiological studies in Japanese printers, there may be an interaction between 1,2-dichloropropane and other chlorinated solvents (e.g., dichloromethane) with regard to the development of cholangiocarcinoma (CCA) (Kubo et al. 2014a, 2014b; Kumagai et al. 2013, 2014, 2016; Sobue et al. 2015; Yamada et al. 2014, 2015a, 2015b). However, available data are inadequate to determine the existence and/or nature of the potential interaction (e.g., one chemical may induce CCA on its own, regardless of co-exposure with additional chlorinated solvents).

In animals, the joint toxicity of 1,2-dichloropropane was assessed with a variety of different compounds; however, these studies lack adequate study design and/or reporting to independently evaluate results. Pozzani et al. (1959) determined that 1,2-dichloropropane has an additive toxic effect when given orally or by inhalation to rats with 1,1,2-trichloroethane, and when given with both ethylene dichloride and perchloroethylene (LD_{50} assessed). Drew et al. (1978) reported that inhalation of 1,2-dichloropropane in combination with trichloropropane by rats did not result in a greater-than-additive toxic effect with regards to hepatic serum enzyme changes (elevated ALT, AST, and ornithine carbamyl transferase levels). Sidorenko et al. (1976, 1979) determined that inhalation of 1,2-dichloropropane has an additive effect in rats and mice when given in combination with 1,2,3-trichloropropane and perchloroethylene with regard to toxic effects on lung, liver, and nervous system.

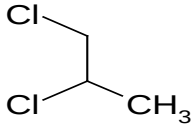
Several studies have evaluated potential adverse effects of inhalation, oral, or dermal exposure to mixtures of dichloropropanes and dichloropropenes (e.g., soil fumigant D-D); however, studies were not designed to evaluate potential interactions between the chemical components (Linnett et al. 1988; Nater and Gooskens 1976; Parker et al. 1982; Shell Oil Co. 1982, 1983).

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

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

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

Characteristic	Information	Reference
Chemical name	1,2-Dichloropropane	MacBean 2010
Synonym(s)	Propylene dichloride; propylene chloride; PDC; dichloro-1,2- propane; DCP; alpha, beta-dichloropropane; alpha, beta propylene dichloride; dichloropropane	ChemIDplus 2017; MacBean 2010; OECD 2006
Registered trade name(s)	Nematox; Vidden D; Dowfume EB-5; 1,2-D; D-D; Telone; Telone II; Component of: D-D Mixture; Nemex; Vidden D; Vorlex	Ali et al. 1986; Bennett 1981; EPA 1995; NPIRS 2017; OECD 2006
Chemical formula	$C_3H_6Cl_2$	MacBean 2010
Chemical structure		ChemIDplus 2017
Identification numbers:		
CAS Registry Number	78-87-5; 26198-63-0 racemic mixture	ChemIDplus 2017; Haynes et al. 2014

[a]Includes names of those products which contain 1,2-dichloropropane in a mixture of compounds.

CAS = Chemical Abstracts Service

4.2 PHYSICAL AND CHEMICAL PROPERTIES

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

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

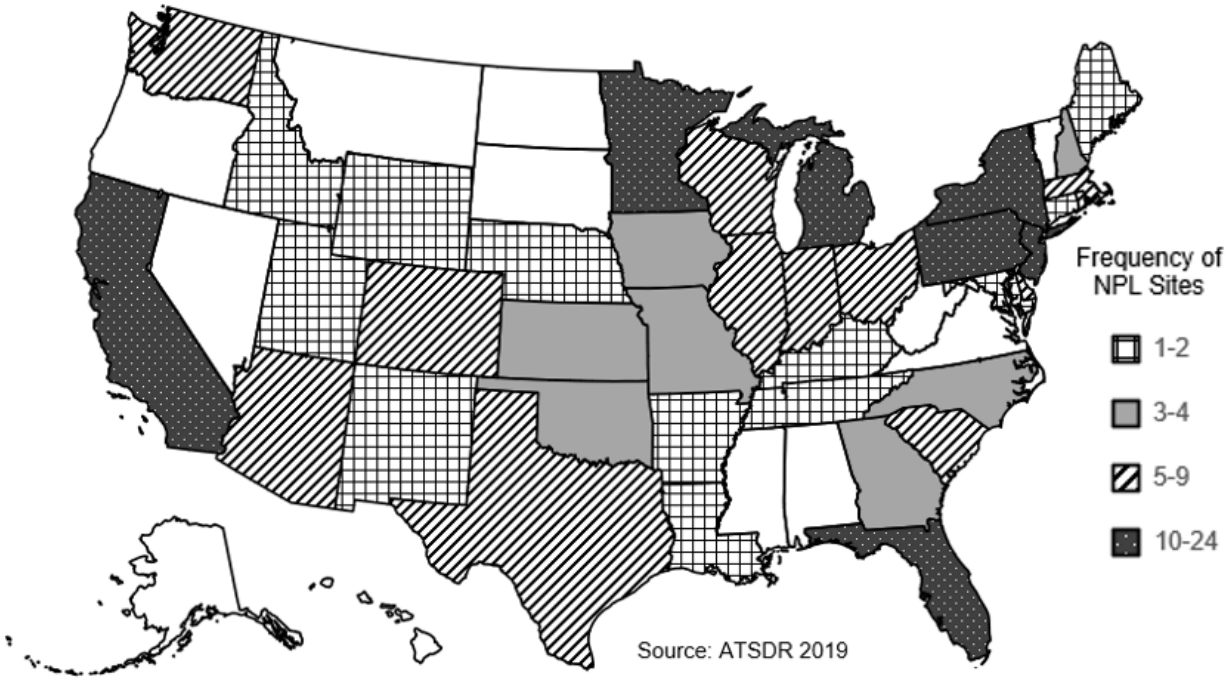
Property	Information	Reference
Molecular weight	112.98	O'Neil et al. 2013
Color	Colorless	OECD 2006
Physical state	Liquid	Haynes et al. 2014
Melting point	-100.44°C Freezes at -70°C	Langer et al. 2011 MacBean 2010
Boiling point	96.3°C	Larranga et al. 2016
Density at 20°C	1.1583	Larranga et al. 2016
Odor	Chloroform-like	Larranga et al. 2016
Odor threshold:		
Water	0.010 ppm (w/v)	Amoore and Hautala 1983
Air	0.25 ppm (v/v)	Amoore and Hautala 1983
Solubility:		
Water at 20°C	2,700 mg/L	MacBean 2010
Water at 25°C	2,800 mg/L	Horvath 1982
Organic solvents	Soluble in ethanol, diethyl ether, benzene, and chloroform	Haynes et al. 2014
Partition coefficients:		
Log K_{ow}	1.98	EPA 2012
Log K_{ow}	2.28	MacBean 2010
Log K_{oc}	1.67	EPA 2012
Vapor pressure at 20°C	53.3 mm Hg (25°C)	EPA 2012
Henry's law constant at 25°C	2.82×10^{-3} at 25°C 2.07×10^{-3} atm-m^3/mol (24°C) 1.67×10^{-3} atm-m^3/mol (24°C)	EPA 1987a Mackay and Yeun 1983 Chiou et al. 1980
Autoignition temperature	557°C	Larranga et al. 2016
Flashpoint	16.1°C 21°C (open cup)	Larranga et al. 2016 O'Neil et al. 2013
Conversion factors	1 mg/m^3=0.21 ppm (v/v)	
Explosive limits	In air: 3.4–14.5 vol %	Langer et al. 2011

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

1,2-Dichloropropane has been identified in at least 231 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 1,2-dichloropropane has been evaluated is not known. The number of sites in each state is shown in Figure 5-1. Of these sites, 230 are located within the United States and 1 is located in Puerto Rico (not shown).

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



- Data indicate that the major use of this substance in consumer products has been diminished, minimizing the potential for exposure to 1,2-dichloropopane in the general population. The most likely route of exposure for the general public to 1,2-dichloropropane is through inhalation of contaminated ambient air and ingestion of waters contaminated with this substance, or through dermal contact with consumer products containing this substance.

- The majority of 1,2-dichloropropane in the environment is a result of anthropogenic activity. This substance is found in the atmosphere as a result of emissions from facilities that produce or use 1,2-dichloropopane and in terrestrial and aquatic environments.

- The general population may be exposed to low levels of 1,2-dichloropropane through inhalation of contaminated ambient air, consumption of contaminated drinking water, or dermal contact.

- Occupational exposure is primarily by inhalation and dermal contact where this substance is produced or used; however, this exposure is limited due to its use in primarily closed systems.

- Volatilization is an important fate process for 1,2-dichloropropane in terrestrial and aquatic environments. In the atmosphere, slow degradation is expected to occur via reaction with photochemically-produced hydroxyl radicals. Due to the slow nature of photodegradation, transport of this chemical from point sources may be possible before it degrades or is washed out of the atmosphere.

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 PRODUCTION

In 1980–1984, the U.S. production of 1,2-dichloropropane was 59.8–77 million pounds (EPA 1995; IARC 1986), of which >95% was used onsite as a captive chemical intermediate in the production of perchloroethylene and other chlorinated products (Dow Chemical Co. 1983; EPA 1986). The 2012 Chemical Data Reporting (CDR) website updated in June 2014, which reports information on the production and use of chemicals manufactured or imported into the United States for 2010 and 2011, lists three companies as producing 1,2-dichloropropane, including Dow Chemical in Freeport, Texas, Dow Chemical in Midland, Michigan, and Dow Chemical in Plaquemine, Louisiana (EPA 2016b). Specific production volume data are listed as confidential business information (CBI), not available (N/A), or 0 for these companies. The 2016 CDR website, which reports information on the production and use of chemicals manufactured or imported into the United States for 2012, 2013, and 2014, listed two parent companies for 1,2-dichloropropane, The Dow Chemical Company with three facilities (Freeport, Texas; Midland, Michigan; Plaquemine, Louisiana) and Olin Corporation with two facilities (Freeport, Texas; Clayton, Missouri) (EPA 2017a). Aggregate production data for 1,2-dichloropropane during the years 2012 through 2015 are reported as withheld in the 2016 CDR (EPA 2017a). Global production for 2001 has been reported as approximately 350 kilotonnes (OECD 2006).

Dow Chemical discontinued production of soil fumigants containing 1,2-dichloropropane in 1991, and pesticide formulations containing this chemical are no longer available in the United States (EPA 1995; IARC 2017; Meister 1987; OECD 2006). In 2019, five consumer/commercial products and three industrial products believed to be currently on the market listed 1,2-dichloropropane as an ingredient on their Safety Data Sheet (SDS). The consumer products were waxes for natural stones, waxes to protect and brighten surfaces, wax in paste, brightener wax for natural stone, and a sealer. The products

contained 1–50% 1,2-dichloropropane (EPA 2020a). The industrial products were flame retardants, containing <0.002–0.0005% 1,2-dichloropropane. The majority of this substance is used on-site or as a limited transport co-product/raw material for the production of other chlorinated compounds (Dow Chemical Co. 1983; EPA 1986; OECD 2006).

High-purity 1,2-dichloropropane is obtained commercially as a byproduct in the manufacture of propylene oxide in the chlorhydrin process. 1,2-Dichloropropane may also be obtained as a byproduct from the synthesis of allyl chloride (Langer et al. 2011). The high-purity product may also be obtained by the reaction of propylene and chlorine in the presence of an iron oxide catalyst at moderate temperature (45°C) and pressure (25–30 psia). Pesticide products that contain 1,2-dichloropropane were distillates of the chlorination of propylene (IARC 1986).

Table 5-1 summarizes information on U.S. companies that reported the manufacture or use of 1,2-dichloropropane in 2018 (TRI18 2020). Toxics Release Inventory (TRI) data should be used with caution since only certain types of industrial facilities are required to report. This is not an exhaustive list.

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

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AR	1	100,000	999,999	12
KY	1	1,000	9,999	12
LA	5	10,000	9,999,999	1, 3, 4, 5, 6, 12, 13, 14
MI	1	1,000	9,999	11
OH	1	1,000	9,999	12
TX	3	0	49,999,999	1, 2, 3, 4, 5, 6, 9, 12, 13
VA	1	100,000	999,999	10
WV	1	10,000	99,999	1, 5, 13

[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

Limited information was found concerning U.S. imports and exports of 1,2-dichloropropane. Import/ export information for 1,2-dichloropropane in the 2016 CDR database, lists one of the five reporting sites as an importer, with import volume reported as 'withheld' (The Dow Chemical Company in Midland, Michigan) (EPA 2017a). Descartes Datamyne, a commercial trade database that reports global import-export data, reported the following companies as importers of 1,2-dichloropropane between 2012 and 2018: Dow Chemical; Evonik Degussa; Fastco Inc., Laredo, Texas; Feria Associates, Laredo, Texas; Hasson House Food Products Inc., Medford, New Jersey; ICL, St. Louis, Missouri; Phoenix Aromas Essential Oils, Norwood, New Jersey; and Witt Management Group, Crystal Lake, Illinois (EPA 2020a). Imports are reported by number of shipments, which do not specify the volume of imports. Dow Chemical Co. imported a total of 144 shipments during this time period. The other companies imported one or two total shipments (EPA 2020a). Reported imports do not necessarily reflect that the companies are currently importing or using 1,2-dichloropropane.

5.2.3 USE

1,2-Dichloropropane is used as a chemical intermediate, in the manufacture of chlorinated solvents, and as an industrial solvent for material such as plastics, fats, and oils, and as an intermediate in rubber processing. Of the five facilities that produce 1,2-dichloropropane, three report that 1,2-dichloropropane is used as a reactant in all other basic organic chemical manufacturing (The Dow Chemical Company; The Dow Chemical Company, Freeport; Olin Blue Cube, Freeport, Texas), one reports that 1,2-dichloropropane is incorporated into a formulation, mixture, or reaction product for all other chemical product and preparation manufacturing (The Dow Chemical Company), and one did not report usage data to the 2016 CDR (EPA 2020a). Other reported uses include as a textile spot remover, paraffin remover, scrubbing agent ingredient, cleanser/degreaser, and galvanizer. 1,2-Dichloropropane was formerly used as a soil fumigant pesticide. The EPA pesticide registration for 1,2-dichloropropane was discontinued in the 1980s, with the last registration ending in 1989. As of September 2020, there were no federally active products listed on the National Pesticide Information Retrieval System (NPIRS) website that contain this chemical as an active ingredient; however, this chemical is a minor impurity (0.06–0.1% by weight) in EPA-registered pesticides containing the active ingredient, dichloropropene (CASRN 542-75-6) (EPA 1998; Langer et al. 2011; NPIRS 2017; OECD 2006; O'Neil et al. 2013).

5.2.4 DISPOSAL

Incineration under controlled conditions for disposal of 1,2-dichloropropane wastes is the most recommended method (EPA 1981). Disposal using a liquid injection incinerator requires a temperature range of 650–1,600°C and residence time of 0.1–2 seconds. A rotary kiln incinerator requires a temperature range of 820–1,600°C and a residence time of seconds. A fluidized bed incinerator requires a temperature range of 450–980°C and a residence time of seconds (EPA 1981). Where disposal of waste residue containing 1,2-dichloropropane is sought, environmental regulatory agencies should be consulted on acceptable disposal practices as it is considered toxic waste subject to disposal regulations, permit, and notification (WHO 1992). 1,2-Dichloropropane may also be a constituent of wastewater streams where it would be susceptible to removal by air stripping (EPA 1986).

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 16,725 pounds (~7.59 metric tons) of 1,2-dichloropropane to the atmosphere from 13 domestic manufacturing and processing facilities in 2018, accounted for about 93% 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 1,2-Dichloropropane[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AR	1	0	0	0	0	0	0	0	0
KY	1	162	0	0	0	0	162	0	162
LA	5	1,373	127	0	477	0	1,977	380	2,357
MI	1	0	0	0	0	0	0	0	0
OH	1	0	0	0	0	0	0	0	0
TX	2	4,402	124	0	4	0	4,530	0	4,530
VA	1	3,802	46	0	0	0	3,848	0	3,848
WV	1	6,986	7	0	0	0	6,993	83	7,076
Total	13	16,725	304	0	481	0	17,510	463	17,973

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

RF = reporting facilities; UI = underground injection

Source: TRI18 2020 (Data are from 2018)

Section 112 of the Clean Air Act (CAA) lists 1,2-dichloropropane as one of the original 189 hazardous air pollutants (HAPs) known to cause or suspected of causing cancer or other serious human health effects or ecosystem damage (EPA 2000). EPA's National Emission Inventory (NEI) database contains comprehensive and detailed estimates regarding sources that emit criteria air pollutants and their precursors, and HAPs for the 50 United States, Washington DC, Puerto Rico, and the U.S. Virgin Islands. The NEI database includes point and nonpoint source emissions, onroad sources, nonroad sources, and event sources such as emissions from wildfires. According to data from the 2017 NEI, 71,871 pounds of 1,2-dichloropropane were released from fuel combustion, industrial processes, solvent degreasing and

industrial coating solvent use, bulk gasoline terminals, and waste disposal (EPA 2014a). These data are summarized in Table 5-3.

Table 5-3. 1,2-Dichloropropane Emissions as Reported by the 2017 National Emission Inventory[a]

Release source	Emissions (pounds)
Industrial processes, storage and transfer	3,935.13
Industrial processes, chemical manufacturing	14,459.52
Fuel combustion, industrial boilers, ICEs; biomass	15,724.75
Industrial processes, oil and gas production	15,689.60
Waste disposal	8,000.44
Fuel combustion, industrial boilers; natural gas	7,043.80
Fuel combustion, electric generation; biomass	3,096.47
Industrial processes, not elsewhere classified	851.21
Industrial processes, pulp and paper	831.41
Fuel combustion, commercial/institutional; biomass	688.61
Fuel combustion, electric generation; coal	547.70
Fuel combustion, industrial boilers, ICEs; other	265.83
Fuel combustion, industrial boilers, ICEs; coal	119.36
Industrial processes, ferrous metals	93.07
Fuel combustion, commercial/institutional; natural gas	73.65
Fuel combustion, electric generation; other	53.31
Industrial processes, cement manufacturing	64.27
Fuel combustion, industrial boilers, ICEs; oil	48.73
Fuel combustion, commercial/institutional; other	32.76
Solvent, industrial surface coating and solvent use	25.48
Industrial processes, non-ferrous metals	46.56
Solvent, degreasing	8.04
Fuel combustion, electric generation; natural gas	12.47
Industrial processes; petroleum refineries	8.60
Fuel combustion, electric generation; oil	0.20
Bulk gasoline terminals	150.03

ICEs = internal combustion engines

Source: EPA 2014a

5.3.2 Water

Estimated releases of 304 pounds (~0.14 metric tons) of 1,2-dichloropropane to surface water from 13 domestic manufacturing and processing facilities in 2018, accounted for about 1.69% of the estimated

total environmental releases from facilities required to report to the TRI (TRI18 2020). These releases are summarized in Table 5-2.

The total estimated annual environmental release of 1,2-dichloropropane in wastewater from production and industrial use was 198,000 pounds (EPA 1986). Table 5-4 shows the types of industries that discharged 1,2-dichloropropane, their frequency of release, and concentrations in wastewater. These data come from a comprehensive wastewater survey conducted by EPA's Effluent Guidelines Division. Over 4,000 samples of wastewater from a broad range of industrial facilities and publicly owned treatment works were analyzed in this survey. Between 1980 and 1988, 708 samples of wastewater in EPA's STORET database were analyzed for 1,2-dichloropropane (WQP 2017a). Ten percent of the samples were ≥10 ppb with a maximum level of 910 ppb. Unfortunately, the detection limit was apparently recorded when no chemical is detected, so it is impossible to say whether the 90th percentile figure represents positive samples or merely higher detection limits.

Table 5-4. Sources of 1,2-Dichloropropane Effluents

		Concentration (ppb)		
Industry	Frequency	Maximum	Medium	Low
Paint and ink	3	3,457.22	38.9176	29.30
Organics and plastics	2	15.93	38.92	6.25
Inorganic chemicals	14	54.30	3.31	0.74
Textile mills	2[a]	40.43	38.76	37.09
Plastics and synthetics	1	5.60	5.60	5.60
Rubber processing	1	0.82	0.82	0.82
Auto and other laundries	1	66.92	66.92	66.92
Pesticides manufacture	1	0.90	0.90	0.90
Photographic industries	3	121.79	36.34	3.59
Organic chemicals	16	1,411.98	23.67	1.23
Publicly owned treatment works	4	52.22	24.86	1.94
Industry unknown	4	60.03	27.07	22.44

[a]Incorrectly listed as 1 reference; data are consistent with a frequency of 2.

Source: Shackelford et al. 1983

1,2-Dichloropropane was found at concentrations of 5.6, 22, 60, and 310 ppb in four outfalls from the Dow Chemical of Canada plant into the St. Clair River for a net loading of 11.8 kg/day (King and Sherbin 1986). This survey was performed because puddles of chlorinated hydrocarbons were discovered on the bottom of the St. Clair River. These chemicals are thought to be products or byproducts of chlorinated hydrocarbons manufactured at this site. Waste from this operation is now being incinerated, but it was

historically landfilled. Landfill leachate was treated with carbon and then discharged into the St. Clair River. The concentrations of 1,2-dichloropropane in the landfill leachate before and after treatment were 320 and 510 ppb, respectively (King and Sherbin 1986). The study authors indicated that the carbon filter was reportedly saturated at the time of the survey, which could account for the increased levels of 1,2-dichloropropane after treatment.

In 1979, the daily amount of 1,2-dichloropropane discharged on 5 days ranged from 37.2 to 5,100 pounds (Weston 1980). The report covering the discharges in 1979 stated that on 4 days, Rohm and Haas contributed all of the 1,2-dichloropropane influent going into Philadelphia's Northeast Water Pollution Control Plant (NEWPCP). On one day, 35% came from elsewhere. At times, all of the 1,2-dichloropropane was removed in the treatment plant. Tidal excursions of the NEWPCP effluents affected the intake of the Baxter Drinking Water Plant, located 2 miles upstream on the Delaware River. EPA's Philadelphia Geographic Area Pollutant Survey found that the average 1,2-dichloropropane concentration in the intake water during 1982–1983 was 1.6 ppb, indicating that 1,2-dichloropropane was being discharged from the wastewater treatment plant into the Delaware River (EPA 1986). If the typical daily discharge from the Rohm and Haas plant was 500 pounds, then the annual discharge would have been 182,000 pounds, a figure approaching the estimated 198,000 pounds of 1,2-dichloropropane discharged into waterways for all production and industrial use. It is not clear for what year the estimated environmental release figure applies and whether the releases into water include industrial discharges that may undergo treatment before being discharged into a waterway or only that which is discharged into a waterway. As of January 1989, Rohm and Haas discontinued use of 1,2-dichloropropane in the manufacture of ion exchange resins (Rohm and Haas 1989). 1,2-Dichloropropane was only detected in one sample at 3 ppb from Eugene, Oregon in the National Urban Runoff Program, which analyzed runoff in 86 samples from 19 cities throughout the United States (Cole et al. 1984).

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 2014b). 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 1,2-dichloropropane above the detection limit of 0.5 µg/L (EPA 2014c, 2014d, 2014e).

5.3.3 Soil

Estimated releases of 481 pounds (~0.22 metric tons) of 1,2-dichloropropane to soils from 13 domestic manufacturing and processing facilities in 2018, accounted for about 2.68% of the estimated total environmental releases from facilities required to report to the TRI (18 2020). No 1,2-dichloropropane was released via underground injection (TRI18 2020). These releases are summarized in Table 5-2.

The total estimated annual environmental release of 1,2-dichloropropane by industry into land disposal sites was 176,000 pounds (EPA 1986). This is not the recommended method of disposal and this figure may have been much higher in the past.

In the past, the major source of release of 1,2-dichloropropane into soil was from its use as a soil fumigant for nematodes. For this purpose, the fumigant was injected into the root zone, after which the soil was compacted to enhance retention of the vapor. However, 1,2-dichloropropane is no longer permitted to be used in the United States for agricultural purposes because this use pollutes groundwater.

Production of 1,2-dichloropropane for use as a solvent in consumer products such as paint strippers, varnishes, and furniture finish removers, from which inadvertent releases to soil (i.e., spills) would be expected, has been discontinued. In addition to spills, chemicals can be released into soil from leaking storage tanks. A case of groundwater contamination by 1,2-dichloropropane resulting from a leaking underground storage tank at a paint factory has been documented in the literature (Botta et al. 1984).

Releases into the subsoil and groundwater can also result from the landfilling of process residues. Four out of 11 samples of landfill leachate in Minnesota and Wisconsin contained 2.0–81 ppb 1,2-dichloropropane (Sabel and Clark 1984).

5.4 ENVIRONMENTAL FATE

5.4.1 Transport and Partitioning

Air. Based on its high vapor pressure, lack of functional groups that absorb at wavelengths above 290 nm, relatively slow photodegradation with photochemically-produced hydroxyl radicals, and half-lives >16 days, atmospheric transport of 1,2-dichloropropane from point sources may be possible before it degrades or is washed out of air. The relatively high water solubility of 1,2-dichloropropane suggests that washout by rain should be an important process for removing this chemical from the atmosphere.

Water. The dominant removal process for 1,2-dichloropropane from surface waters is expected to be volatilization. Based on the measured relative mass transfer coefficient of 1,2-dichloropropane between water and air of 0.57 (Cadena et al. 1984) and the range of reaeration coefficients typical of relatively rapid and shallow streams found in the western United States, 0.14–1.96 $hour^{-1}$ (Cadena et al. 1984), the half-life of 1,2-dichloropropane in these streams will range from 0.62 to 8.68 hours. The residence time in a lake or pond would be much longer. Based on a measured Henry's Law constant at 25°C of $2.82x10^{-3}$ atm-m^3/mol (EPA 1987a), 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 speed is estimated to be 4.3 days; the volatilization half-life of 1,2-dichloropropane in a model river 1 m deep flowing 1 m/second with a wind speed of 3 m/second is estimated to be 3.4 hours (EPA 2012), with resistance in the liquid phase controlling volatilization (Thomas 1982). In such cases, the current will have a much greater effect on volatilization than the wind speed. In wastewater treatment plants that receive volatile compounds such as 1,2-dichloropropane from industrial discharges or other sources, stripping will be an important mechanism for transferring the chemical from the water into the air. In stripping, as opposed to ordinary volatilization, the liquid and gas phases are dispersed with the result that the interfacial surface area is much greater and liquid/gas mass transfer is greatly enhanced. More than 99% removal of 1,2-dichloropropane from wastewater plants has been attributed to the stripping process (Kincannon et al. 1983).

Sediment and Soil. The measured K_{oc} of 1,2-dichloropropane is 47 in a silt loam soil (Chiou et al. 1979). This value is low, suggesting that 1,2-dichloropropane will not adsorb appreciably to soil, sediment, or suspended solids in water. 1,2-Dichloropropane sorbs to clay minerals in dry soil but desorbs when the soil is moist (Cohen et al. 1984). 1,2-Dichloropropane has been used as a soil fumigant for nematodes in California and the coastal areas of Georgia, South Carolina, North Carolina, and Virginia, where soils are sandy and have a low organic carbon content (Cohen et al. 1984). Adsorption to these soils will be lower than to soils with a higher organic content; therefore, the mobility of 1,2-dichloropropane will not be reduced significantly. The leaching potential of 1,2-dichloropropane is illustrated by a case study in California in which a soil core was taken from an agricultural field where a fumigant containing the chemical had recently been used. Residues of 1,2-dichloropropane up to 12.2 ppb were detected throughout much of the 24-foot core profile and two adjacent drinking water wells contained concentrations of 1,2-dichloropropane in excess of 10 ppb (Ali et al. 1986). As much as 300 ppt of 1,2-dichloropropane have been detected in bank-filtered Rhine River water, indicating that not all of the chemical was being retained by the soil (Piet and Morra 1979). The finding that highly mobile and biologically resistant residues of the fumigant pesticide 1,2-dibromoethane persisted in topsoil for

years after application, despite its mobility and volatility, spurred a study of this phenomenon in other halogenated hydrocarbons (Sawhney et al. 1988). Sandy loam soils treated with 10,000 ppm of 1,2-dichloropropane for 1 day were extracted 16 times with water. The apparent soil-water partition coefficient, initially 0.56 (K_{oc} 22), rose to 72 (K_{oc} 2,800); the final concentration of 1,2-dichloropropane in the soil was 1.4 ppm. After a 57-day period, the apparent partition coefficient was >250 (K_{oc} >9,700). Some of the 1,2-dichloropropane molecules were adsorbed more strongly than others, and these molecules became even more strongly adsorbed in time. The fact that pulverization of the soil released a portion of the chemical suggests that the strongly adsorbed 1,2-dichloropropane eventually became occluded in the soil structure. Additionally, these observations suggest that the rate at which the chemical becomes occluded, or the adsorption coefficient increases, is diffusion controlled.

The dissipation of 1,2-dichloropropane was determined in two clay and two sandy soils in closed systems following application at normal field rates (van Dijk 1980). The mean dissipation rate was 0.013 day^{-1} (half-life 52 days), with the rate roughly twice as high in the sandy soil as in the clay soil. Additionally, the rate of volatilization increased by a factor of 2 for a 10°C increase in temperature. In another experiment in which 1,2-dichloropropane was mixed with 3 cm of soil in an open container, covered with 12 cm of soil and left outdoors, <1% of the chemical remained after 10 days (Roberts and Stoydin 1976). This loss was attributed to volatilization.

Other Media. A bioconcentration factor (BCF) of 9 in fish has been estimated for 1,2-dichloropropane using linear regression equations with estimated measured log K_{ow} of 1.98 (EPA 2012; Thomas 1982). Experimental BCF values of 3.2 and 2.5 were calculated for carp (*Cyprinus carpio*) exposed to 1,2-dichloropropane (0.4 ppm) over a 4- and 6-week period, respectively (NITE 2017a). An experimental value for the BCF of <10 has also been reported (Kawasaki 1980). These BCF data suggest that 1,2-dichloropropane is expected to have very low potential for bioconcentration in fish.

When potatoes were grown in sandy loam soil that had been treated with a mixture of ^{14}C-labeled 1,2-dichloropropane and 1,3-dichloropropene 5 months before sowing, only 7 ppb of the radioactivity was found in the mature potatoes indicating minimal uptake of either of these chemicals (Roberts and Stoydin 1976).

5.4.2 Transformation and Degradation

Air. The primary mode of degradation in air is through reaction with photochemically-produced hydroxyl radicals by H-atom abstraction (Singh et al. 1982). Experimental determinations of the reaction rate yield a half-life of >23 days (Atkinson 1985), whereas theoretical estimates result in a half-life of 16 days (Atkinson 1985). Lacking a chromophore that absorbs radiation >290 nm, direct vapor-phase photolysis would not be expected. Accordingly, no photolysis occurred when 1,2-dichloropropane was exposed to simulated sunlight for prolonged periods of time (Cohen et al. 1984).

Water. 1,2-Dichloropropane is resistant to hydrolysis, with an estimated hydrolysis half-life of 25–200 weeks (Cohen et al. 1984). Most studies indicated that 1,2-dichloropropane is also resistant to biotransformation. No degradation was observed in a semicontinuous activated sludge process after 10 weeks, even when the retention time was as long as 25 hours (Shell Oil Co. 1984). There was also no degradation in two standard 4-week tests that simulated biodegradability in environmental waters (Anonymous 1983; Kawasaki 1980). While >99% of 1,2-dichloropropane was lost in a wastewater treatment facility, the loss was attributed to stripping, rather than biodegradation (Kincannon et al. 1983).

Sediment and Soil. Based on limited data, biodegradation of 1,2-dichloropropane may not be a rapid fate process; however, it may occur under certain conditions in sediment and soil. When 71 ppm of radiolabeled 1,2-dichloropropane was applied to a sandy loam soil and a medium loam soil in closed glass containers and incubated for 20 weeks, <0.2% of the applied radioactivity was found in degradation products (Roberts and Stoydin 1976). Using the Japanese MITI test, 1,2-dichloropropane present at 100 mg/L, reached 0% of its theoretical biological oxygen demand (BOD) in 2 weeks using an activated sludge inoculum at 30 mg/L (NITE 2017b). 1,2-Dichloropropane, present at 5 and 10 mg/L, achieved 42 and 36% biodegradation, respectively, after 7 days of incubation in the dark at 25°C using a static culture screening test with microbial inoculum from a sewage treatment plant (Tabak et al. 1981). 1,2-Dichloropropane was completely degraded to propene after 4 months under anaerobic conditions with enrichment cultures derived from river sediments at temperatures between 20 and 25°C (Loffler et al. 1997). Nonmethanogenic *Dehalococcoide* and *Dehalobacter* species obtained from river sediments have been attributed to the biotransformation of 1,2-dichloropropane to propene via dichloroelimination (Fletcher et al. 2009; Ritalahti and Loffler 2004; Schlötelburg et al. 2002). Biotransformation rates of approximately 2.57 and 1.08 µmoles/day were calculated from experiments under anaerobic conditions using two *Dehalococcoide* cultures; biotransformation of >90% radiolabeled 1,2-dichloropropane to

propene was observed after 6 and 11 days, following initial lag phases of 3 and 15 days, respectively (Fletcher et al. 2009).

Other Media. Atmospheric contaminants may accumulate on terrestrial vegetation. Air-to-vegetation transfer of 1,2-dichloropropane was investigated using a *Lycopersicon esculentum* fruit cuticular matrix at 25°C. The matrix/air partition coefficient experimentally determined for 1,2-dichloropropane was approximately 770, indicating a propensity towards intermediate partitioning (Welke et al. 1998).

5.5 LEVELS IN THE ENVIRONMENT

No natural sources of 1,2-dichloropropane have been identified (IARC 2017). Therefore, levels in the environment are due to anthropogenic activity. Reliable evaluation of the potential for human exposure to 1,2-dichloropropane depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of 1,2-dichloropropane in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on 1,2-dichloropropane 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 5-5 shows the lowest limit of detections that are achieved by analytical analysis in environmental media.

Table 5-5. Lowest Limit of Detection of 1,2-Dichloropropane Based on Standards

Media	Detection limit	Reference
Air	0.2–10 ppb	De Bortoli et al. 1986; EPA 1999, 2002; NIOSH 1994; Shikiya et al. 1984
Drinking water	0.018–0.17 ppb	Comba and Kaiser 1983; EPA 1982a, 1986, 2009
Surface water and groundwater	0.01–5 ppb	EPA 1987b, 1995
Soil	1 ng/g	NEMI 1998
Sediment	1 ng/g	NEMI 1998
Whole blood	0.008–0.012 ppb	Ashley et al. 1992, 1994

An overview summary of the range of concentrations detected in environmental media is presented in Table 5-6.

Table 5-6. Summary of Environmental Levels of 1,2-Dichloropropane

Media	Low	High	Reference
Outdoor air (ppt)	<2	724	McCarthy et al. 2006; OECD 2006
Indoor air (ppbv)	Trace	0.46	Pellizzari 1982
Water (ppm)		<50	OECD 2006
Surface water (ppb)	0.5	2.5	WQP 2017b
Ground water (ppb)	0.000001	5,000	WQP 2017b
Drinking water	Not detected		WQP 2017b
Soil/sediment (ppb)	Not detected	1,700,000	WQP 2017b

Detections of 1,2-dichloropropane in air, water, and soil at NPL sites are summarized in Table 5-7.

Table 5-7. 1,2-Dichloropropane Levels in Water, Soil, and Air of National Priorities List (NPL) Sites

Medium	Median	Geometric mean	Geometric standard deviation[a]	Number of quantitative measurements	NPL sites
Water (ppb)	10	21.4	24.1	73	51
Soil (ppb)	260	996	73.9	12	11
Air (ppbv)	0.539	3.39	149	12	11

[a]Concentrations found in ATSDR site documents from 1981 to 2019 for 1,867 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

1,2-Dichloropropane has been detected in ambient air. The highest concentrations were found near point sources or directly after application of products containing this chemical. Outdoor and indoor air monitoring data for 1,2-dichloropropane have been compiled in Tables 5-8 and 5-9.

Table 5-8. Outdoor Air Monitoring Data for 1,2-Dichloropropane

Location(s)	Geographic type	Date(s)	Range	Mean concentration	Notes	Reference
United States	Urban/suburban	Not specified (1982 or earlier)	22–110 ppt	57 ppt (median)	Detected in 396 U.S. samples	EPA 1982b
United States	City	Not specified (1982 or earlier)	21–78 ppt		24-Hour sampling for 1–2 weeks in seven U.S. cities	Singh et al. 1982
San Jose, California; Downey, California; Houston, Texas; Denver, Colorado	Urban	1984–1985	<2–724 ppt			Singh et al. 1992
California	City	Not specified (1984 or earlier)	0.2–1,100 ppt		Only 2% of the levels monitored were >0.2 ppt; one site had a high of 1,100 ppt; four sites monitored by the California Air Monitoring Program	Shikiya et al. 1984
Portland, Oregon		Not specified (1985 or earlier)	4.4–8.4 ppt		Measured during rain events	Ligocki et al. 1985
United States	Industrial or source-related sites	Not specified (1982 or earlier)	0–130 ppt	120 ppt (median)	39 Sites monitored	EPA 1982b
Philadelphia, Pennsylvania	Source-related sites	Not specified (1985 or earlier)		259 ppt	3-Month survey of 10 source-related sites	Sullivan et al. 1985

Table 5-8. Outdoor Air Monitoring Data for 1,2-Dichloropropane

Location(s)	Geographic type	Date(s)	Range	Mean concentration	Notes	Reference
Philadelphia, Pennsylvania	City		40,740 ppt in various sections of the city; 77,000–120,000 ppt downwind of plant		Northeast Water Pollution Control Plant had received discharges from the Rohm and Haas plant, which produced ion exchange resins using 1,2-dichloropropane as a solvent	EPA 1986
United States		January–December 2016	0.000027–0.121 ppb	Mean 0.0025 ppb median 0.119 ppb	Detected in 25 out of 128 samples: Philadelphia, Pennsylvania; Essex, Maryland; Beltsville, Maryland; Asheville, North Carolina; Burlington, Vermont; North Laurel, Maryland; Baltimore, Maryland; Underhill, Vermont; Rutland, Vermont; Terre Haute, Indiana; Hopewell, Virginia; Portland, Oregon; East Highland Park, Virginia; Calvert City, Kentucky; Medford, Oregon; Los Angeles, California; Grapevine, Texas; Rubidoux, California; Davie, Florida	EPA 2016c
United States	Various ambient air monitoring sites; industrial; near roads	January–December 2017	0–1.00 ppb	Mean 0.0023 ppb median 0	Arizona; California; Colorado; Delaware; District of Columbia; Florida; Georgia; Illinois; Indiana; Kentucky; Maryland; Massachusetts; Michigan; Minnesota; Missouri; North Carolina; New Jersey; New York; North Carolina; Ohio; Oklahoma; Oregon; Pennsylvania; Rhode Island; South Carolina; Texas; Utah; Vermont; Virginia; Washington; West Virginia; Wisconsin (10,768 samples)	EPA 2020b
United States	Various ambient air monitoring sites; industrial; near roads	January–December 2015	0–1.74 ppb	Mean 0.0035 ppb median 0	Indiana; Michigan; North Carolina; Texas; Pennsylvania; Minnesota; Vermont; Utah; Virginia; Wisconsin; Oregon; Oklahoma; West Virginia; Maryland; Delaware; Kentucky; Colorado; Florida; California;	EPA 2017b

Table 5-8. Outdoor Air Monitoring Data for 1,2-Dichloropropane

Location(s)	Geographic type	Date(s)	Range	Mean concentration	Notes	Reference
					District of Columbia; New Jersey; Missouri; Arizona; Illinois; Georgia; Iowa; Ohio; New York; Rhode Island; Massachusetts (11,295 samples)	
United States	Various ambient air monitoring sites; industrial; near roads	January–December 2010	0–3.67 ppb	Mean 0.0048 ppb median 0	Iowa; Texas; Wyoming; Virginia; Oregon; West Virginia; Wisconsin; Florida; North Carolina; California; Indiana; Minnesota; Pennsylvania; District of Columbia; Maryland; Delaware; South Carolina; New York; New Jersey; Arizona; Rhode Island; Massachusetts; Mississippi; Missouri; New Mexico; Georgia; Hawaii; Illinois; Alabama; Colorado; Michigan; Maine; Ohio; Kentucky; Washington; Vermont; Utah; Oklahoma; South Dakota; Tennessee (11,945 samples)	EPA 2017b
United States	Various ambient air monitoring sites; industrial; near roads	January–December 2005	0–10.42 ppb	Mean 0.0089 ppb median 0	Indiana; Virginia; Oregon; Texas; Ohio; California; South Carolina; Florida; Vermont; New York; Wisconsin; North Carolina; Washington; Idaho; Maryland; Pennsylvania; New Jersey; Arizona; Minnesota; New Hampshire; Delaware; District of Columbia; West Virginia; Maine; Massachusetts; Georgia; Illinois; Louisiana; Michigan; Iowa; Puerto Rico; Alabama; Colorado; Rhode Island; North Dakota; Utah; Oklahoma; South Dakota; Tennessee; Mississippi; Missouri (14,254 samples)	EPA 2017b
United States	Various ambient air monitoring sites; industrial; near roads	January–December 2000	0–8 ppb	Mean 0.0098 ppb median 0	Washington; Indiana; Maine; Florida; Texas; Louisiana; New York; Oregon; Pennsylvania; Maryland; Virginia; Minnesota; District of Columbia; Delaware; Michigan; Colorado; Massachusetts; Iowa; Rhode Island; Vermont; Utah; Wisconsin;	EPA 2017b

Table 5-8. Outdoor Air Monitoring Data for 1,2-Dichloropropane

Location(s)	Geographic type	Date(s)	Range	Mean concentration	Notes	Reference
					South Dakota; New Jersey; Ohio; North Dakota (8,184 samples)	
United States	Various ambient air monitoring sites; industrial; near roads	January–December 1995	0–10.14 ppb	Mean 0.051 ppb median 0	Indiana; Texas; Pennsylvania; Vermont; Maryland; Minnesota; Louisiana; Washington; Illinois; Alabama; New Jersey; Tennessee; Michigan (2,097 samples)	EPA 2017b
United States	Various ambient air monitoring sites; industrial; near roads	January–December 1991	0–10.14 ppb	Mean 0.028 ppb median 0	New Jersey; Florida; Illinois; District of Columbia; Texas; Louisiana; Tennessee; Maryland; Kansas; Virginia (644 samples)	EPA 2017b

Table 5-9. Indoor Air Monitoring Data for 1,2-Dichloropropane

Location(s)	Geographic type	Date(s)	Range/mean concentrations	Notes	Reference
Montana	Residential, rural, and urban		Below reporting limit of 0.46 µg/m^3	Indoor air of 50 non-smoking homes without vapor intrusion issues	MDEQ 2012
Old Love Canal in Niagara Falls, New York	Residential	Not reported (1980 or earlier)	Trace (indoor); 0.29 ppb (one basement)	Indoor air of nine homes	Barkley et al. 1980; Pellizzari 1982
Edison, New Jersey	Industrial waste disposal site	Not reported (1982 or earlier)	Not detected		Pellizzari 1982
Iberville Parish, Louisiana	Industrial		Traces to 0.46 ppb	Several organic chemical producers, users, and storage facilities are located along this section of the Mississippi River	Pellizzari 1982

5.5.2 Water

1,2-Dichloropropane has been detected in surface water, well water, and groundwater. Monitoring data indicate a decrease of the detectable concentrations in the environment over the past few decades, most likely a result of the discontinuation of several use categories. Water monitoring data for 1,2-dichloro-propane have been compiled in Table 5-10.

Table 5-10. Water Monitoring Data for 1,2-Dichloropropane

Location(s)	Geographic type	Date(s)	Range	Mean concentration	Notes	Reference
Lake Ontario		Not reported (1983 or earlier)	Trace–440 ppt		Detectable concentrations in 19 of 95 monitoring stations	Kaiser et al. 1983
Lower Niagara River		Not reported (1983 or earlier)	Trace–55 ppt		Detectable concentrations in 9 of 16 monitoring stations	Kaiser et al. 1983
California	Finished water	June 2010–June 2012	Not detected		Data collected by U.S. Geological Survey (USGS) California Water Science Center	WQP 2017b
Grenada, Mississippi	Industrial related site	January 2016	Not detected		Not detected at or above the detection limit, 0.50 µg/L (ppb)	EPA 2016d
United States	Surface water	January 2010–December 2016	0.5–2.5 µg/L (ppb)	Mean: 0.6 µg/L (ppb); median 0.5 µg/L (ppb)	Data collected by USGS monitoring stations across the United States; mean and ranges do not reflect samples reported as not detected/below detection limit	WQP 2017b
United States	Surface water	Not reported		1.2 mg/L	Data collected at a site following application of this chemical as a pesticide	OECD 2006
Ohio River, United States	Surface water	Not reported (1979 or earlier)		0.1 ppb	Identified in 1.6% of samples from 11 water utilities	EPA 1980
United States	Surface water	Not reported (1984 or earlier)	0.9 and 21 ppb		Detectable concentrations in 13 of 945 water supplies from groundwater sources	Westrick et al. 1984
Suffolk County, New York	Surface water	Not reported (1983 or earlier)	Not reported	Not reported	Detectable concentrations in 0.9% of 575 community water supplies from groundwater sources; detectable concentrations in 5.5% of 19,000 non-community and private wells	SCDHS 1983

Table 5-10. Water Monitoring Data for 1,2-Dichloropropane

Location(s)	Geographic type	Date(s)	Range	Mean concentration	Notes	Reference
United States	Surface water	1980–1988	≥0.40–300 ppb		Detectable concentrations in 10% of 29,320 samples	WQP 2017a
California	Well water	1982	Trace–1,200 ppb		Detectable concentrations in 75 wells in 9 counties; 12 wells exceeded the state's action level of 10 ppb	Cohen 1986; Ali et al. 1986
Western Washington	Well water	Not reported (1986 or earlier)			Detectable concentrations in seven shallow wells near soil injection in strawberry fields	Cohen 1986
United States	Domestic wells	1996–2002	~0.02–>10 µg/L		Detected at concentrations >5 µg/L in 3 of 2,400 wells; detected in 9 of 1,207 domestic well samples analyzed by USGS's low-level analytical method and reported with no censoring of data	Rowe et al. 2007
Minnesota	Groundwater underlying landfills	Not reported (1984 or earlier)	0.5–43 ppb		Detectable concentrations in groundwater samples underlying soil/sand/clay landfills	Sabel and Clark 1984
Colorado	Groundwater underlying major urban center (Denver)	1993	<0.2 ug/L		Detected at concentrations of <0.2 ug/L (method detection limit) in 1 of 30 wells	Bruce and McMahon 1996
United States	Groundwater	January 2010–December 2016	0.000001–5,000 µg/L (ppb)	Mean: 12.6 µg/L (ppb); median 1 µg/L (ppb)	Data collected by USGS monitoring stations across the United States; mean and ranges do not reflect samples reported as not detected	WQP 2017b
United States	Groundwater	1980–1988	3–1,500 ppb		Concentrations above 3 ppb in 10% of 22,457 samples	WQP 2017a

Table 5-10. Water Monitoring Data for 1,2-Dichloropropane

Location(s)	Geographic type	Date(s)	Range	Mean concentration	Notes	Reference
United States	Source water samples; 569 groundwater and 373 surface water samples (170 river, 203 reservoir)	May 3, 1999 to October 23, 2000	<0.2		Not detected above the method detection limit	USGS 2003

5.5.3 Sediment and Soil

1,2-Dichloropropane has been detected in sediment and soil. Concentrations in soil are likely a direct result of its former use as a soil fumigant. Soil and sediment monitoring data for 1,2-dichloropropane have been compiled in Table 5-11.

Table 5-11. Soil and Sediment Monitoring Data for 1,2-Dichloropropane

Location(s)	Geographic type	Date(s)	Range/mean concentrations	Notes	Reference
United States	Sediment	1980–1988	>44 ppb	Concentrations above 3 ppb in 10% of 859 samples	WQP 2017a
California	Soil		Up to 12.2 ppb	From soil cores underlying a recently fumigated field	Ali et al. 1986
California	Soil		0.2–2.2 ppb	From soil cores up to 7 m below the surface	Cohen et al. 1984
Salt Chuck Mine, State of Alaska	Subsurface soil/sediment	July 16, 2011	4.6–19 µg/kg (ppb)	Depth 2–4 feet	WQP 2017b
Big Valley Band of Pomo Indians of the Big Valley Rancheria, California	Sediment	April 2011–May 2011	Not detected	Depth 0.152 m	WQP 2017b
City and county of Honolulu	Sediment	January 2010–September 2014	Not detected	Depth 57.9–75.3 m	WQP 2017b
EPA Great Lakes National Program	Sediment	April 2011–October 2011	5–1,700,000 µg/kg (ppb)	Depth 0–10.3 m; mean 46,600 µg/kg (ppb); median: not detected/less than detection limit of specific sampling method used	WQP 2017b

5.5.4 Other Media

No monitoring data for 1,2-dichloropropane were identified for flora or fauna collected from the environment in the United States. Based on partition coefficient data (see Section 5.4), there is potential for atmospheric 1,2-dichloropropane to accumulate on terrestrial vegetation (Welke et al. 1998).

Monitoring data collected by the City and County of Honolulu in January 2010, January 2011, January 2012, January 2013, and January 2014 reported that 1,2-dichloropropane was not detected in liver or muscle tissue samples collected from the following fish species: *Lutjanus kasmira*, *Selar crumenophthalmus*, and *Myripristis berndti* (WQP 2017b).

5.6 GENERAL POPULATION EXPOSURE

Results from the NHANES show that concentrations of 1,2-dichloropropane in whole blood samples were below the detection limit of 0.008 ng/mL for study years 2003–2004 and 2005–2006 in 1,364 and 3,120 members of the U.S. general population, respectively. Concentrations in whole blood samples for study years 2007–2008 and 2009–2010 were below the detection limit of 0.01 ng/mL in 2,840 and 3,255 members of the U.S. general population, respectively. For the most recent available study years, 2011–2012, concentrations of 1,2-dichloropropane in whole blood samples were below the detection limit of 0.01 ng/mL in 2,740 members of the U.S. general population (CDC 2019). The evaluation of general population exposure levels is limited by the detection limits of the analytical method employed by NHANES (Kirman et al. 2012). However, Kirman et al. (2012) and Aylward et al. (2010) indicate that the whole blood analytical method used to collect NHANES data is sensitive enough to detect recent toxicologically relevant exposures.

A National Occupational Exposure Survey (NOES) conducted by NIOSH from 1981 to 1983 estimated that 2,944 workers, including 1,022 women, were potentially exposed to 1,2-dichloropropane in the United States (NOES 1990). The distribution of these estimated exposed workers by standard industrial category (SIC) was: 408 in business services, 1,656 in machinery (except electrical), 161 in fabricated metal products, 672 in the chemical and allied products, and 47 in textile mill products. The estimate was provisional, as all the data for trade name products that may contain 1,2-dichloropropane had not been analyzed. The NOES was based on field surveys of 4,490 facilities and was designed as a nationwide survey based on a statistical sample of virtually all workplace environments in the United States where eight or more persons were employed in all SIC codes except mining and agriculture. The use pattern of 1,2-dichloropropane has changed radically since the survey was conducted, as it has been eliminated from

agricultural fumigants, photographic film manufacture, and paint strippers. Therefore, the estimate of the number of exposed workers reported by the NOES is expected to be an overestimate of the current occupational exposure scenario, despite exclusion of agricultural workers. Another category of workers who may be exposed to 1,2-dichloropropane are those at wastewater treatment facilities that handle effluent containing this chemical. Volatilization would be expected during treatment operations. According to Dow Chemical Company, the major manufacturer of 1,2-dichloropropane, all processes involving the production, conversion, and disposal of 1,2-dichloropropane are closed processes (Dow Chemical Co. 1983). By their estimates, 45 and 123 workers are routinely and potentially exposed, respectively, to the chemical (Dow Chemical Co. 1983). The levels of exposure reported are <2 ppm for toluene diisocyanate production, <1 ppm in ion exchange resin manufacture, and <25 ppm in paper coating (Dow Chemical Co. 1983). According to the 2016 Toxic Substances Control Act (TSCA) Inventory Update Reporting data, five reporting facilities under two parent companies, Dow Chemical and Olin Corporation, estimate that the number of workers reasonably likely to be exposed during the manufacturing, processing, or use of 1,2-dichloropropane in the United States may be as low as fewer than 10 workers and as high as at least 50 but fewer than 100 workers per plant; the data may be greatly underestimated due to confidential business information (CBI) or unknown values (EPA 2017a).

According to drinking water surveys conducted in the mid-1980s (Ali et al. 1986; Cohen 1986; EPA 1980; Westrick et al. 1984), a significant number of drinking water supplies contained 1,2-dichloropropane, and people drinking this water would have been exposed to this chemical. In the most broadly-based groundwater survey, 1.4% of these supplies contained median water concentrations of 0.9 ppb (Westrick et al. 1984). People drinking this water would ingest 1.8 µg of 1,2-dichloropropane/day. While most of the drinking water supplies tested for 1,2-dichloropropane were taken from groundwater sources, in cities such as Philadelphia, Pennsylvania, which obtains its water from a river that received sizeable amounts of 1,2-dichloropropane-containing effluent, the concentration of 1,2-dichloropropane in the drinking water from the Baxter Drinking Water Plant averaged 1.5 ppb (EPA 1986). People consuming this water would have ingested 3.0 µg of 1,2-dichloropropane daily.

The general population is exposed to 1,2-dichloropropane in ambient air. Reported mean measured ambient air concentrations in the United States were 0.0025 ppb in 2019, 0.0023 ppb in 2017, 0.0048 ppb in 2010, 0.0089 ppb in 2005, 0.0098 ppb in 2000, and 0.051 ppb in 1995 (EPA 2017b). Residents of Philadelphia, according to EPA's Philadelphia Geographic Area Multimedia Pollutant Survey, would have been exposed to much higher inhalation levels up to 0.12 ppb, with an estimate intake of 98–660 µg/day, because a large user of 1,2-dichloropropane was located there (EPA 1986). People living in

the vicinity of landfills containing 1,2-dichloropropane may be exposed to 1,2-dichloropropane present in landfill gases. Not enough information is available to estimate what the level of exposure from this source might be. Subsurface and surface emissions of VOCs have been found from RCRA Subtitle D disposal sites, which reportedly received only non-hazardous waste. However, hazardous waste from small quantity generators or household hazardous waste may be disposed of at these landfills. For landfills that are similar in design and content, emissions are estimated to be a factor of 2.6 greater in a wet climate than in a dry one (Vogt et al. 1987).

About 45% of 1,2-dichloropropane volatilizes from water while showering (ATSDR 2020). Volatility from other household uses of water range from about 20% (sinks, toilets) to 65% (dishwashers) (ATSDR 2020). 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-Use Exposure (SHOWER) model predicts air concentrations in the shower stall, bathroom, and main house throughout the day by estimating the contribution from showering or bathing and the contribution from other water sources in the house, such as the dishwasher, clothes washer, and faucets. This information, along with human activity patterns, is used to calculate a daily TWA exposure concentration via inhalation exposure and from dermal uptake from skin contact. ATSDR's SHOWER model is available by sending a request to showermodel@cdc.gov.

Vapor intrusion may also be a potential source of 1,2-dichloropropane exposure, as vapor intrusion has been observed for several volatile organic chemicals (VOCs) with similar properties. EPA's compilation of five studies of background indoor air concentrations found a 0–2% detection rate for 1,2-dichloro-propane in 1,050 U.S. resident samples between 1990 and 2005 (EPA 2011). The background medians and 95th percentiles were below the reporting limits, which ranged from 0.04 to 2.31 µg/m^3, and maximum values ranged from less than the reporting limit to 34 µg/m^3. ATSDR did not find 1,2-dichloropropane to exceed any ATSDR vapor intrusion comparison values from air, soil gas, or groundwater in a review of 148 public health assessments published between 1994 and 2010 (Burk and Zarus 2013).

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Those people consuming contaminated drinking water will have the greatest potential for exposure to 1,2-dichloropropane. Since the odor threshold for 1,2-dichloropropane is 10 ppb (Amoore and Hautala 1983), people consuming water with this level of 1,2-dichloropropane may detect a chloroform-like odor,

which could provide a warning that their water is contaminated. In general, drinking water supplies that are most apt to be contaminated are those taken from groundwater sources. Contaminated drinking water wells are most likely to be found in agricultural areas with sandy soil where the chemical was used as a fumigant. However, there are special situations, such as in Philadelphia, where drinking water derived from surface water sources may be contaminated with 1,2-dichloropropane-containing effluent. In Philadelphia, 1,2-dichloropropane-containing effluent from an industrial plant was driven upstream to the influent of a drinking water plant by tidal action. This plant recently discontinued using 1,2-dichloropropane. People residing in the vicinity of industrial sources may be exposed to 1,2-dichloropropane in the ambient air, either from direct emissions or volatilization of the chemical from wastewater. Although industrial uses of 1,2-dichloropropane have decreased, workers who use 1,2-dichloropropane as a chemical intermediate (even in a “closed” system) are still considered a potentially high exposure group.

CHAPTER 6. ADEQUACY OF THE DATABASE

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

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

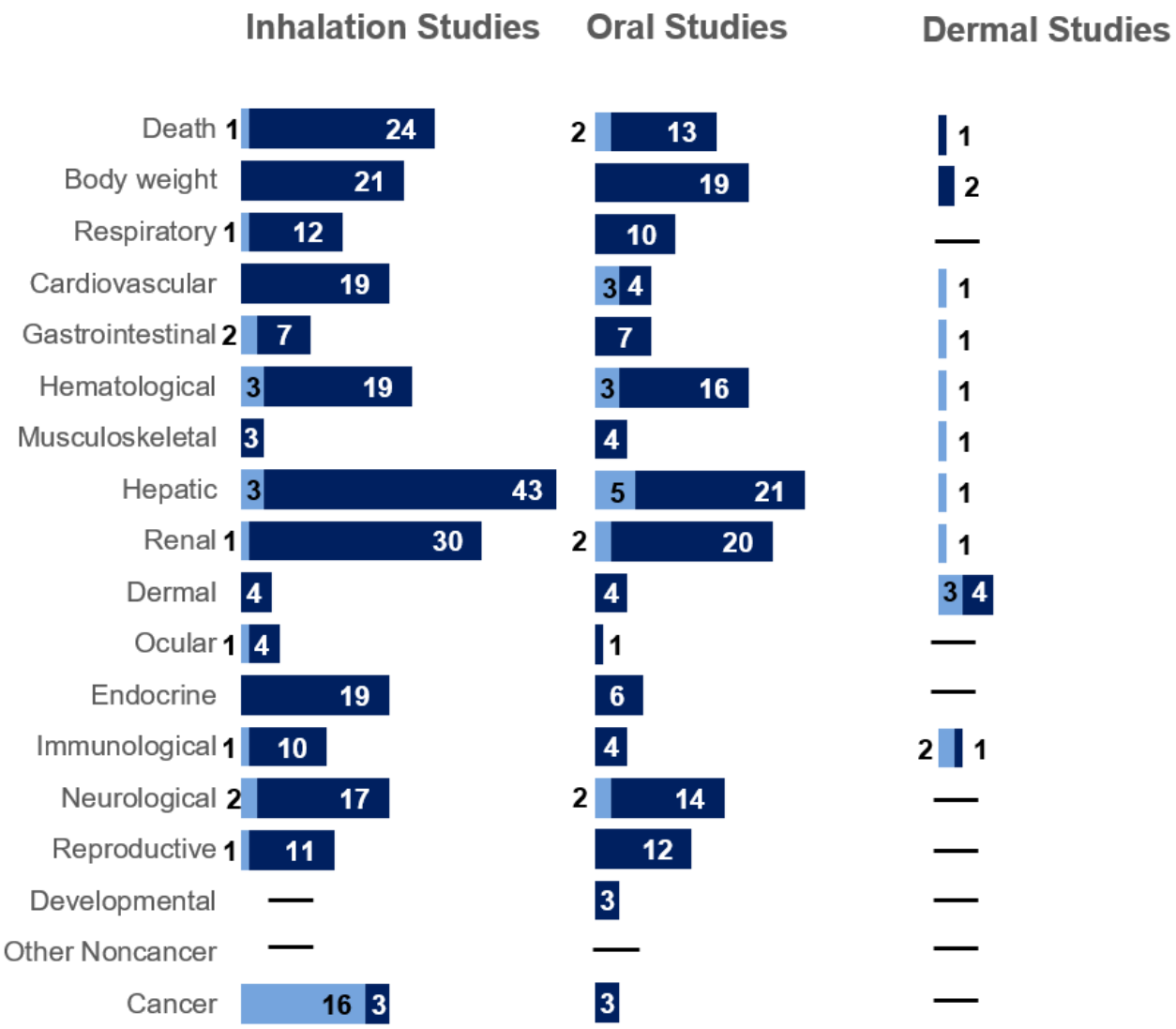
6.1 Information on Health Effects

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

As illustrated in Figure 6-1, most of the data on the toxicity of 1,2-dichloropropane come from inhalation studies in laboratory animals, although several oral studies in laboratory animals are also available. The most commonly examined endpoints were hepatic, renal, and body weight effects. The available human studies include several epidemiological studies evaluating cancer in workers exposed to 1,2-dichloropropane, in which exposure is expected to be predominantly via inhalation. Data on noncancer effects in humans are primarily from case reports of accidental or intentional acute oral, inhalation, and/or dermal exposure to high levels of 1,2-dichloropropane. The laboratory animal dermal toxicity database consists of a small number of studies evaluating limited endpoints.

Figure 6-1. Summary of Existing Health Effects Studies on 1,2-Dichloropropane By Route and Endpoint

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



*Includes studies discussed in Chapter 2. A total of 113 studies (including those finding no effect) have examined toxicity; most animal studies examined multiple endpoints.

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 inhalation database is adequate to derive an acute-duration inhalation MRL. Additional low-concentration studies designed to identify a NOAEL for the critical effect (upper respiratory lesions) in the most susceptible species (rat) could decrease uncertainty in the acute-duration inhalation MRL. The oral database is adequate to derive an acute-duration oral MRL.

Intermediate-Duration MRLs. The inhalation database is adequate to derive an intermediate-duration inhalation MRL. Additional low-concentration studies designed to identify a NOAEL for the critical effect (upper respiratory lesions) could decrease uncertainty in the intermediate-duration inhalation MRL. The oral database is adequate to derive an intermediate-duration oral MRL.

Chronic-Duration MRLs. The inhalation database is inadequate to derive a chronic-duration inhalation MRL. Available chronic inhalation studies identified LOAEL concentrations for the critical effect (nasal lesions) at levels >5-fold higher than the lowest LOAEL for nasal lesions identified in intermediate-duration studies. Low-concentration studies designed to identify a NOAEL for the critical effect (nasal lesions) could potentially identify a point of departure (POD) to use as the basis for a chronic-duration inhalation MRL. The oral database is inadequate to derive a chronic-duration oral MRL. Chronic studies providing data at low doses are needed.

Health Effects. Identification of data needs for health effects in animal studies is limited to targets included in the systematic review with animal data needs.

> ***Respiratory.*** The upper respiratory tract has been identified as a sensitive target following acute-, intermediate-, and chronic-duration inhalation exposure in animals; however, a NOAEL for repeated exposure has not been established. Additional low-concentration studies designed to identify a NOAEL for upper respiratory lesions are needed. Studies designed to determine the

mechanism of nasal lesion toxicity could be useful for determining the human relevance of these findings.

Renal. While human case studies indicate that the kidney may be a target of 1,2-dichloropropane toxicity, supporting animal data are inconsistent or lacking. Human epidemiological studies and/or additional animal studies designed to evaluate renal toxicity following exposure, particularly renal function, may be useful.

Developmental. Developmental toxicity data are only available from a limited number of oral studies. Additional studies evaluating specialized developmental effects (e.g., neurotoxicity) as well as developmental effects following inhalation exposure would be useful to address this data gap. Also, since available data only report developmental effects at doses that elicit parental toxicity, studies designed to assess whether developmental effects are secondary to parental toxicity may be useful.

Epidemiology and Human Dosimetry Studies. Epidemiology studies are limited to case studies of accidental or intentional exposure, one case-control study evaluating potential associations with atopic dermatitis, and occupational case studies and retrospective cohort studies evaluating cancer in Japanese printers. A common limitation of these studies is the lack of control for the presence of other chlorinated solvents, many of which have similar toxic endpoints as 1,2-dichloropropane. Additional epidemiology studies controlling confounding exposures and examining endpoints that have been shown to occur at low doses in laboratory animals (respiratory, hematological, hepatic, neurological, and developmental effects) would be useful. In the absence of additional epidemiological studies, studies designed to evaluate potential mechanisms of action (MOAs), particularly cancer MOAs, would be useful to determine the relevance of animal findings.

Biomarkers of Exposure and Effect. Available data suggest that unchanged 1,2-dichloropropane in the urine or blood or glutathione conjugated metabolites in the blood may be appropriate biomarkers of exposure. While current analytical methods used to detect unchanged 1,2-dichloropropane in the blood are not sensitive enough to detect background levels in the general population, Kirman et al. (2012) and Aylward et al. (2010) indicate that the whole blood analytical method used to collect NHANES data is sensitive enough to detect recent toxicologically relevant exposures. Additional research is needed to validate extrapolation of biomarker levels to external exposure doses.

Absorption, Distribution, Metabolism, and Excretion. The toxicokinetics of 1,2-dichloropropane in rats are relatively well characterized following oral and inhalation exposure. Additional studies following dermal exposure and/or in different species would address this data need.

Comparative Toxicokinetics. No studies were found that evaluated differences in toxicokinetics between species. Toxicokinetic studies in different species may be useful to determine if toxicokinetic differences may explain observed species differences (increased susceptibility to nasal lesions in rats, potentially increased susceptibility to renal lesions in mice). Qualitative and quantitative comparison of human metabolites with those of animals could help identify the most appropriate species to serve as a model for predicting toxic effects in humans and for studying the mechanisms of action.

Children's Susceptibility. No human data are available regarding children's susceptibility. Available data from oral developmental studies do not indicate that developing animals are uniquely susceptible to toxicity following exposure to 1,2-dichloropropane. Developmental effects have not been evaluated in animals following inhalation exposure. 1,2-Dichloropropane is primarily metabolized by CYP2E1, which is fully developed in children, but it is not known if there would be toxicodynamic differences between children and adults that might influence susceptibility. Experimental studies in young animals and/or epidemiological data for children would be useful to address these data gaps.

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

Production, Import/Export, Use, Release, and Disposal. Information on production, uses, and releases of 1,2-dichloropropane are available and have been discussed in Chapter 5. Data indicate that use of this substance in consumer products has been diminished. 1,2-Dichloropropane is not sold for direct consumer use; this substance is mainly used onsite or as a limited transport co-product/raw material for the production of other chlorinated compounds. Limited information is available concerning U.S. imports and exports of 1,2-dichloropropane. Disposal practices are regulated by environmental regulatory agencies. Further data do not appear to be essential at this time.

Environmental Fate. Sufficient data exist to show that chemical hydrolysis and aerobic biodegradation of 1,2-dichloropropane are very slow and are not significant in determining the half-life in surface water or soil. Additional studies of anaerobic biotransformation could be useful in estimating the half-life of 1,2-dichloropropane in soil and groundwater. Experimental hydrolysis data at pH 5–9 would

be helpful for predicting the half-life of 1,2-dichloropropane in groundwater where volatilization is not significant.

Bioavailability from Environmental Media. Since 1,2-dichloropropane was phased out as a fumigant and its use in solvents has declined, recent monitoring data are needed for air, groundwater, and surface water. This is particularly important with respect to groundwater, where it is especially persistent and may be present in significant concentrations. Field monitoring studies of 1,2-dichloropropane would also be useful. This may be the only feasible way of determining the half-life of 1,2-dichloropropane in groundwater. Air monitoring and surface water studies would show the effects of changing 1,2-dichloropropane use patterns. While EPA's STORET database contains considerable water monitoring data, there are problems with the database that limit its usefulness. The detection limit is apparently recorded when no chemical is detected, so that it is impossible to say whether the 90^{th} percentile figures for surface water and groundwater provided in Section 5.3.2 represent positive determinations or merely detection limits. It would be helpful, when quantitative data cannot be obtained, if these monitoring data would indicate whether 1,2-dichloropropane was qualitatively detected in the samples.

Food Chain Bioaccumulation. 1,2-Dichloropropane has not been reported in food or in organisms collected from the environment. No studies investigating uptake of this chemical in animals were located, and experimental studies in plants are limited to a single study in potatoes. An experimentally determined BCF of 3.2 in carp, along with the estimated BCF of 9, indicate that there is a very low potential for bioaccumulation in the food chain.

Exposure Levels in Environmental Media. Monitoring data indicate a decrease of the detectable concentrations in the environment over the past few decades, most likely as a result of the discontinuation of several use categories. Section 112 of the Clean Air Act (CAA) lists 1,2-dichloropropane as one of the original 189 HAPs known to cause or suspected of causing cancer or other serious human health effects or ecosystem damage. Continued monitoring would be beneficial in assessing the potential risk for environmental exposure. There are little or no monitoring data regarding 1,2-dichloropropane on vegetation and flora; these data would be useful as there is the potential for dermal exposure to individuals handling plant material near contaminated sites that may contain 1,2-dichloropropane due to atmospheric deposition.

Exposure Levels in Humans. The use pattern of 1,2-dichloropropane has changed radically since NIOSH's NOES survey. Since the elimination of 1,2-dichloropropane from agricultural fumigants, photographic film manufacture, and paint strippers, fewer workers are exposed. While agricultural workers were not included in the survey, those engaged in the manufacture of agricultural chemicals were included. As a chemical in paint strippers, 1,2-dichloropropane would have a particularly high potential for exposing large numbers of people at high levels of exposure, since such applications are labor intensive and performed in the open. Therefore, the results of the NOES will have to be reanalyzed in light of current use patterns in order to reflect current occupational exposures. People living in the vicinity of landfills containing 1,2-dichloropropane and hazardous waste sites may be exposed to 1,2-dichloropropane present in off-gases. Not enough information is available to estimate what the level of exposure from this source might be. Data correlating levels in biological samples with media exposure levels and the subsequent development of health effects are especially needed for populations living in the vicinity of hazardous waste sites.

Exposures of Children. Children may be exposed to 1,2-dichloropropane through the same routes as adults. However, occupationally exposed workers are at greater risk of exposure to higher levels of 1,2-dichloropropane than the general U.S. population. Monitoring of children's exposure to 1,2-dichloropropane would be useful, in combination with children's health and susceptibility information, to assess the potential risk for deleterious effects.

6.3 Ongoing Studies

One ongoing epidemiological study of 1,2-dichloropropane was identified by the National Institutes of Health (NIH) (RePORTER 2020). This study, summarized in Table 6-1, is the ongoing Sister Study prospective cohort evaluating potential associations between air toxics and breast cancer.

Table 6-1. Ongoing Studies on 1,2-Dichloropropane

Investigator	Affiliation	Research description	Sponsor
Dale P. Sandler	National Institutes of Health	Potential associations between air toxics and breast cancer; Sister Study prospective cohort	NIEHS

NIEHS = National Institute of Environmental Health Sciences

Source: RePORTER 2020

CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding 1,2-dichloropropane in air, water, and other media are summarized in Table 7-1. This table is not an exhaustive list, and current regulations should be verified by the appropriate regulatory agency.

ATSDR develops MRLs, which are substance-specific guidelines intended to serve as screening levels by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. See Section 1.3 and Appendix A for detailed information on the MRLs for 1,2-dichloropropane.

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

Agency	Description	Information	Reference
	Air		
EPA	RfC	$4x10^{-3}$ mg/m^3 (0.0009 ppm)	EPA 1991
	Provisional peer reviewed toxicity values		
	Provisional subchronic RfC	$4x10^{-3}$ mg/m^3 (0.0009 ppm)	EPA 2016a
WHO	Air quality guidelines	Not listed	WHO 2010
	Water & Food		
EPA	Drinking water standards and health advisories		EPA 2018a
	10-Day health advisory (10-kg child)	0.09 mg/L	
	10^{-4} Cancer risk	0.06 mg/L	
	National primary drinking water regulations		EPA 2009
	MCL	0.005 mg/L	
	RfD	Not evaluated	EPA 1991
	Provisional peer reviewed toxicity values		EPA 2016a
	Provisional chronic and subchronic RfD	$4x10^{-2}$ mg/kg/day	
WHO	Drinking water quality guidelines		WHO 2017
	Provisional guideline value	0.04 mg/L	
	TDI	14 µg/kg body weight	
FDA	Substances added to food[a]	No data	FDA 2020
	Cancer		
HHS	Carcinogenicity classification	No data	NTP 2016
EPA	Provisional peer reviewed toxicity values		EPA 2016a
	Carcinogenicity classification	Likely to be carcinogenic to humans	
	Provisional inhalation unit risk	$3.7x10^{-3}$ $(mg/m^3)^{-1}$	
	Provisional oral slope factor	$3.7x10^{-2}$ $(mg/kg/day)^{-1}$	
IARC	Carcinogenicity classification	Group 1[b]	IARC 2017

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

Agency	Description	Information	Reference
	Occupational		
OSHA	PEL (8-hour TWA) for general industry, shipyards, and construction	75 ppm (350 mg/m^3)	OSHA 2020a, 2020b, 2020c
NIOSH	REL (up to 10-hour TWA)	Ca[c]	NIOSH 2019
	IDLH	400 ppm[c]	NIOSH 2014
	Emergency Criteria		
EPA	AEGLs-air	Not listed	EPA 2018b
DOE	PACs-air		DOE 2018a
	PAC-1[d]	30 ppm	
	PAC-2[d]	220 ppm	
	PAC-3[d]	2,000 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 from use in food, delisted color additives, and some substances "no longer FEMA GRAS".
[b]Group 1: carcinogenic to humans.
[c]Potential occupational carcinogen.
[d]Definitions of PAC terminology are available from U.S. Department of Energy (DOE 2018b).

AEGL = acute exposure guideline levels; DOE = Department of Energy; EAFUS = Everything Added to Food in the United States; EPA = U.S. Environmental Protection Agency; FDA = Food and Drug Administration; FEMA = Flavor and Extract Manufacturers Association of the United States; GRAS = generally recognized as safe; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; JECFA = Joint FAO/WHO Expert Committee on Food Additives; MCL = maximum contaminant level; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TDI = tolerable daily intake; TWA = time-weighted average; WHO = World Health Organization

CHAPTER 8. REFERENCES

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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*:** 1,2-Dichloropropane
CAS Numbers: 78-87-5
Date: November 2021
Profile Status: Final
Route: Inhalation
Duration: Acute
MRL 0.02 ppm
Critical Effect: Nasal lesions
Reference: Nitschke and Johnson 1983
Point of Departure: 100 ppm minimal LOAEL ($LOAEL_{HEC}$ of 1.8 ppm)
Uncertainty Factor: 90
LSE Graph Key: 9
Species: Rat

MRL Summary: An acute-duration inhalation MRL of 0.02 ppm was derived for 1,2-dichloropropane based on olfactory mucosal degeneration in rats exposed to concentrations ≥100 ppm for 2 weeks (6 hours/day, 4–5 days/week); a no-observed-adverse-effect level (NOAEL) was not identified for nasal effects (Nitschke and Johnson 1983). The MRL is based on the lowest-observed-adverse-effect level (LOAEL) of 100 ppm, which was adjusted to continuous duration exposure and converted to a human equivalent concentration ($LOAEL_{HEC}$) of 1.8 ppm for slight olfactory mucosal degeneration and a total uncertainty factor of 90 (3 for use of a minimal LOAEL, 3 for extrapolation from animals to humans after dosimetric adjustment, and 10 for human variability).

Selection of the Critical Effect: Available data indicate that the upper respiratory system is the most sensitive target for toxic effects following acute-duration inhalation exposure to 1,2-dichloropropane (see Table A-1). Hepatic effects were also considered, but these effects occurred at concentrations 2–4-fold higher than the lowest LOAEL identified for nasal lesions. Of the species evaluated for nasal lesions, the rat was the most sensitive, with a LOAEL of 100 ppm for degeneration of the nasal mucosa (lowest concentrations tested). The LOAEL values for nasal lesions in other species evaluated in this study were higher than the rat LOAEL (300 ppm for mice, 1,000 ppm for rabbits); therefore, the rat is considered the most sensitive species for the critical effect.

Table A-1. Summary of Candidate Critical Effects for Acute Inhalation MRL for 1,2-Dichloropropane

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Nasal effects					
Fischer-344 rat	2 weeks (4–5 days/week; 6 hours/day)	ND	100	Olfactory mucosal degeneration	Nitschke and Johnson 1983
B6C3F1 mouse	2 weeks (4–5 days/week; 6 hours/day)	100	300	Olfactory mucosal degeneration	Nitschke and Johnson 1983
New Zealand rabbit	2 weeks (4–5 days/week; 6 hours/day)	300	1,000	Olfactory mucosal degeneration	Nitschke and Johnson 1983

Table A-1. Summary of Candidate Critical Effects for Acute Inhalation MRL for 1,2-Dichloropropane

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Hepatic effects					
BALB/cA mouse	14 days (6 hours/day)	ND	200	Hepatic vacuolation	Zhang et al. 2015
BALB/cA mouse	7 days (8 hours/day)	ND	300	Hepatic vacuolation	Zhang et al. 2015
C57BL/6J mouse	7 days (8 hours/day)	ND	300	Hepatic vacuolation	Zhang et al. 2015
C57BL/6J mice	1–12 days (7 hours/day)	ND	400	Slight fatty degeneration	Heppel et al. 1948
Golden Syrian hamster	14 days (8 hours/day)	200	400	Slight dilation of hepatic sinusoids	Zhang et al. 2015
Golden Syrian hamster	7 days (8 hours/day)	300	ND	ND	Zhang et al. 2015

LOAEL = lowest observed adverse effect level; MRL = Minimal Risk Level; ND = not determined; NOAEL = no-observed-adverse-effect level

Selection of the Principal Study: The study with the lowest identified LOAEL for the critical effect of nasal lesions was selected as the principal study (Nitschke and Johnson 1983). Of the species tested in this study, the rat was the most sensitive, with a LOAEL of 100 ppm for degeneration of the nasal mucosa (lowest concentrations tested). The LOAEL values for nasal lesions in other species evaluated in this study were 300 ppm for mice and 1,000 ppm for rabbits.

Summary of the Principal Study:

Nitschke KD, Johnson KA. 1983. Propylene dichloride: One day and two week inhalation toxicity in rats. Dow Chemical Company, Midland, MI.

Groups of F344 rats (5/sex) were exposed to 1,2-dichloropropane at concentrations of 0, 100, 300, or 1,000 ppm for 6 hours/day for 9 days over a 2-week period. Animals were observed for signs of toxicity after each exposure period. Body weights were recorded prior to the 1st, 5th, 6th, and 9th exposure. Prior to the 9th exposure, blood was collected for hematology and clinical chemistry. Urine was collected for urinalysis. All surviving animals were sacrificed the day following the final exposure. All animals were examined grossly. The brain, heart, liver, kidneys, thymus, and testes were removed and weighed. The entire respiratory tract (nasal turbinates, larynx, trachea, and lungs), adrenals, liver, kidney, testes, thymus, and bone marrow were examined for histopathological changes.

No deaths or clinical signs of toxicity were observed during the exposure period. All treated rats had significantly reduced body weight gain, which was attributed to reduced food intake by the study authors. No exposure-related hematological effects were observed. Blood chemistry findings were consistent with decreased food intake, and not considered by the study authors to be related to toxicity. Female rats had decreased plasma cholinesterase activities that were not dose related. No effects on urinalysis indices were observed. Relative liver weight was significantly increased by 8–15% in male rats at 1,000 ppm and female rats at 300 and 1,000 ppm; these findings may be exposure related. Other observed organ weight changes were considered secondary to decreased food intake. Olfactory mucosal degeneration was

observed in 100% of rats from all exposure groups, and none of the control rats. The severity of this lesion increased in a dose-related manner, from slight at 100 ppm to severe at 1,000 ppm. Inflammatory and exudative changes were also increased in a dose-related manner in the nasal tissue. No other respiratory tract lesions were observed. Decreased cellularity of bone marrow and thymus observed at 300 and 1,000 ppm is consistent with stress as a result of decreased food intake. The bone marrow changes did not correlate with hematological parameters. Slight hepatocellular hypertrophy in 3/5 female rats exposed to 1,000 ppm is consistent with increased liver weight. No exposure-related histopathologic lesions were observed in kidneys, adrenals, or testes.

Selection of the Point of Departure for the MRL: The LOAEL of 100 ppm for nasal lesions was selected as the POD. This value was considered a minimal LOAEL due to the slight severity of the lesion. The data were not suitable for benchmark dose (BMD) modeling because incidence data went from 0% in the control to 100% in the lowest concentration group.

Adjustment for Intermittent Exposure: The LOAEL was adjusted from intermittent exposure to account for a continuous exposure scenario:

$LOAEL_{ADJ}$ = 100 ppm x (6 hours/24 hours) x (9 days/14 days) = 16 ppm

Human Equivalent Concentration: A human equivalent concentration (HEC) was calculated by multiplying the duration-adjusted LOAEL by the regional gas dose ratio (RGDR) for the extrathoracic region of the respiratory tract. The $RGDR_{ET}$ of 0.115 was calculated using the following equation:

$$RGDR_{ET} = (V_E/SA_{ET})_A/(V_E/SA_{ET})_H$$

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

V_E = 119 mL/minute and SA_{ET} = 15 cm^2 in rats and V_E = 13,800 mL/minute and SA_{ET} = 200 cm^2 in humans (EPA 1994).

$RGDR_{ET}$ = (119 mL/minute ÷ 15 cm^2)/(13,800 mL/minute ÷ 200 cm^2) = 0.115

$LOAEL_{HEC} = LOAEL_{ADJ}$ x $RGDR_{ET}$
$LOAEL_{HEC}$ = 16 ppm x 0.115= 1.8 ppm

Uncertainty Factor: The $LOAEL_{HEC}$ is divided by a total uncertainty factor of 90:

- 3 for use of a minimal LOAEL. The dose was considered a minimal LOAEL because the severity of the lesions was graded as slight.
- 3 for extrapolation from animals to humans after dosimetric adjustment
- 10 for human variability

MRL = $LOAEL_{HEC}$ ÷ UFs
MRL = 1.8 ppm ÷ (3 x 3 x 10) = 0.02 ppm

Other Additional Studies or Pertinent Information that Lend Support to this MRL: The upper respiratory tract is the most sensitive target following both acute- and intermediate-duration inhalation exposure, and the rat is the most sensitive species tested. Olfactory mucosal degeneration was observed in rats and mice exposed to ≥100 ppm and rabbits at 1,000 ppm for 2 weeks (Nitschke and Johnson 1983). In intermediate-duration studies, nasal cavity lesions were observed in rats exposed to ≥15 ppm (lowest concentration tested), including hyperplasia of the respiratory epithelium at ≥15 ppm, degeneration of the olfactory epithelium at ≥50 ppm, atrophy of the olfactory epithelium at ≥125 ppm, submucosal inflammation at ≥150 ppm, and inflammation of the respiratory epithelium at ≥1,000 ppm (Nitschke et al. 1988; Umeda et al. 2010). Intermediate-duration studies also observed nasal lesions in mice at ≥300 ppm (but not ≤200 ppm) (Matsumoto et al. 2013; Nitschke et al. 1988) and rabbits at 1,000 ppm (but not ≤500 ppm) (Nitschke et al. 1988). In chronic studies, nasal lesions were observed in rats at ≥80 ppm (lowest concentration tested), including atrophy of olfactory epithelium, inflammation of the respiratory epithelium, squamous cell metaplasia of respiratory epithelium, hyperplasia of the transitional epithelium, squamous cell hyperplasia, and hyperplasia of the submucosal glands (Umeda et al. 2010) and mice at ≥80 ppm (but not 32 ppm), including atrophy of olfactory epithelium and metaplasia of the olfactory epithelium and submucosal glands (Matsumoto et al. 2013).

Limited evidence from accident reports following chemical spills suggest that inhalation exposure to 1,2-dichloropropane causes respiratory irritation in humans following acute exposure to presumably high concentrations (exposure levels not available) (ACGIH 2014; Rubin 1988).

Agency Contacts (Chemical Managers): Carolyn Harper

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2-Dichloropropane
CAS Numbers: 78-87-5
Date: November 2021
Profile Status: Final
Route: Inhalation
Duration: Intermediate
MRL 0.002 ppm
Critical Effect: Nasal lesions
Reference: Nitschke et al. 1988
Point of Departure: $BMCL_{10}$ of 2.38 ($BMCL_{HEC}$ of 0.05 ppm)
Uncertainty Factor: 30
LSE Graph Key: 35
Species: Rat

MRL Summary: An intermediate-duration inhalation MRL of 0.002 ppm was derived for 1,2-dichloropropane based on hyperplasia of the nasal respiratory epithelium in rats exposed to concentrations ≥15 ppm for 13 weeks (6 hours/day, 5 days/week); a NOAEL was not identified for nasal effects (Nitschke et al. 1988). The MRL is based on the $BMCL_{10}$ of 2.38 ppm, which was adjusted to continuous duration exposure and converted to a human equivalent concentration ($BMCL_{HEC}$) of 0.05 ppm for hyperplastic lesions in male and female rats (combined) and a total uncertainty factor of 30 (3 for extrapolation from animals to humans after dosimetric adjustment and 10 for human variability).

Selection of the Critical Effect: Available data indicate that the upper respiratory system is the most sensitive target for toxic effects following intermediate-duration inhalation exposure to 1,2-dichloropropane (see Table A-2). Other effects considered (hemolytic anemia, altered estrous cycle) occurred at concentrations 6–10-fold higher than the lowest LOAEL identified for nasal lesions; no NOAEL was identified for nasal lesions.

Table A-2. Summary of Candidate Critical Effects for Intermediate Inhalation MRL for 1,2-Dichloropropane

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Respiratory effects[a]					
F344 rat	13 weeks (6 hours/day, 5 days/week)	ND	15	Hyperplasia of nasal respiratory epithelium	Nitschke et al. 1988
F344 rat	13 weeks (6 hours/day, 5 days/week)	ND	125	Hyperplasia of nasal respiratory epithelium and atrophy of olfactory epithelium	Umeda et al. 2010
B6D2F1/Crlj mouse	13 weeks (6 hours/day, 5 days/week)	200	300	Respiratory metaplasia, atrophy, necrosis, and desquamation of nasal cavity	Matsumoto et al. 2013

Table A-2. Summary of Candidate Critical Effects for Intermediate Inhalation MRL for 1,2-Dichloropropane

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Reproductive effects					
F344 rat	21–24 days (8 hours/day)	50	100	Lengthened estrous cycle	Sekiguchi et al. 2002
Hematological effects					
New Zealand rabbit	13 weeks (6 hours/day, 5 days/week)	ND	150	Hemolytic anemia	Nitschke et al. 1988

[a]Selected critical effect.

LOAEL = lowest observed adverse effect level; MRL = Minimal Risk Level; ND = not determined; NOAEL = no-observed-adverse-effect level

Selection of the Principal Study: The study with the lowest identified LOAEL for the critical effect of nasal lesions was selected as the principal study (Nitschke et al. 1988).

Summary of the Principal Study:

Nitschke KD, Johnson KA, Wackerle DL, et al. 1988. Final report on propylene dichloride 13-week inhalation toxicity study with rats, mice and rabbits with cover letter dated 032888. Dow Chemical Company. Submitted to the U.S. Environmental Protection Agency under TSCA Section FYI. OTS0000399-1. FYI-OTS-0488-0399.

Groups of F344 rats (10/sex/group) were exposed to 1,2-dichloropropane (99.94% pure) via whole-body inhalation for 13 weeks (5 days/week, 6 hours/day) at concentrations of 0, 15, 50, or 150 ppm. Endpoints examined included mortality, clinical signs, weekly body weight, eyes (fluorescent illumination), hematology, clinical chemistry, organ weights (brain, heart, liver, kidneys, thymus, testes), and histology for complete set of 47 tissues including the respiratory tract (nasal tissues, larynx, trachea, lungs, and organs normally present on sections with these organs) in control and high-exposure groups. The respiratory tract, liver, gallbladder, kidney, and thymus were also examined in the low- and mid-exposure groups.

There were no exposure-related mortalities or overt signs of toxicity. Body weight gain was significantly lower than controls throughout the study in rats exposed to 150 ppm, but body weight decreases >10% were only observed in males. There were no exposure-related effects on hematological, clinical chemistry, or urinalysis parameters or on organ weights. Hyperplasia of nasal mucosa was observed in 0/10, 2/9, 5/10, and 9/10 males and 0/10, 3/10, 7/10, and 9/10 females at 0, 15, 50, and 150 ppm, respectively. Slight degeneration of olfactory mucosa was observed in rats exposed to 50 and 150 ppm, with inflammation of larynx in males exposed to 150 ppm. No other exposure-related histopathologic lesions were observed. The authors considered hyperplasic lesions of nasal mucosa to be protective response of equivocal toxicological significance; ATSDR generally considers hyperplasic lesions to be an adverse effect. Furthermore, additional nasal lesions are observed at higher concentrations and following longer exposure durations (see Umeda et al. 2010). Therefore, the lowest concentration (15 ppm) was identified as a LOAEL for upper respiratory lesions; no NOAEL was identified.

Selection of the Point of Departure for the MRL: The $BMCL_{10}$ value of 2.38 ppm for increased incidence of nasal respiratory epithelium hyperplasia in male and female rats (combined) was selected as the basis of the MRL.

BMD modeling was performed on the incidence of nasal respiratory epithelium hyperplasia in male and female F344 rats, as well as the combined data for both sexes (Table A-3). The data were fit to all available dichotomous models in EPA's Benchmark Dose Software (BMDS, version 3.1.2) using a benchmark response (BMR) of 10% extra risk. However, dichotomous Hill models were not considered viable because the model has four parameters, requiring at minimum five data points (including control), and these data sets have only four data points. For remaining models, adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, BMCL that is not 10 times lower than the lowest non-zero dose, and scaled residual within ±2 units at the data point (except the control) closest to the predefined BMR. Among all of the models providing adequate fit to the data, the lowest BMCL (95% lower confidence limit on the benchmark concentration) 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's Information Criterion (AIC) was chosen.

Table A-3. Incidence of Nasal Respiratory Epithelium Hyperplasia in F344 Rats Following Inhalation Exposure to 1,3-Dichloropropane for 13 Weeks

	Concentration (ppm)			
	0	15	50	150
Males	0/10 (0%)	2/9 (22%)	5/10 (50%)	9/10 (90%)
Females	0/10 (0%)	3/10 (30%)	7/10 (70%)	9/10 (90%)
Combined	0/20 (0%)	5/19 (25%)	12/20 (60%)	18/20 (90%)

Source: Nitschke et al. 1988

All models except dichotomous Hill provided adequate fit to the increased incidence of nasal lesions in male rats. BMCLs for models providing adequate fit were not sufficiently close (differed by ≥3-fold), so the model with the lowest BMCL was selected (Log-Logistic). The frequentist, restricted Log-Logistic model estimated a BMC_{10} and $BMCL_{10}$ of 9.08 and 2.44 ppm, respectively. The results of the BMD modeling are summarized in Table A-4.

Table A-4. Model Predictions for Incidence of Nasal Respiratory Epithelium Hyperplasia in Male F344 Rats Exposed to 1,2-Dichloropropane for 13 Weeks (Nitschke et al. 1988)

					Scaled residuals[c]	
Model	BMC_{10}[a] (mg/kg/day)	$BMCL_{10}$[a] (mg/kg/day)	p-Value[b]	AIC	Dose near BMC	Dose near control
Dichotomous Hill			0.55	36.27	0.273	-3.90×10^{-4}
Gamma[d]	7.05	4.54	1.00	31.96	-3.90×10^{-4}	-3.90×10^{-4}
Log-Logistic[e,f]	**9.08**	**2.44**	**0.83**	**34.27**	**0.273**	**-3.90×10^{-4}**
Log-Probit[e]	11.59	7.44	0.76	34.41	0.577	-3.90×10^{-4}
Multistage (3-degree)[g]	7.21	4.54	0.97	33.95	-3.90×10^{-4}	-3.90×10^{-4}
Multistage (2-degree)[g]	7.17	4.54	0.97	33.95	-3.90×10^{-4}	-3.90×10^{-4}

Table A-4. Model Predictions for Incidence of Nasal Respiratory Epithelium Hyperplasia in Male F344 Rats Exposed to 1,2-Dichloropropane for 13 Weeks (Nitschke et al. 1988)

Model	BMC_{10}[a] (mg/kg/day)	$BMCL_{10}$[a] (mg/kg/day)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose near BMC	Dose near control
Multistage (1-degree)[g]	7.05	4.54	1.00	31.96	-3.90×10^{-4}	-3.90×10^{-4}
Weibull[d]	7.05	4.54	0.97	33.96	-3.94x10-4	-3.94×10^{-4}
Logistic	21.20	13.30	0.32	37.21	0.399	-1.13
Probit	20.89	13.84	0.32	37.19	0.422	-1.11

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

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

For increased incidence of nasal lesions in female rats, six frequentist, restricted models provided adequate fit to the data. BMCLs for models providing adequate fit were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Multistage 1-, 2-, and 3-degree). The Multistage models, which all converged on the 1-degree model, estimated a BMC_{10} and $BMCL_{10}$ of 5.28 and 3.45 ppm, respectively. The results of the BMD modeling are summarized in Table A-5.

Table A-5. Model Predictions for Incidence of Nasal Respiratory Epithelium Hyperplasia in Female F344 Rats Exposed to 1,2-Dichloropropane for 13 Weeks (Nitschke et al. 1988)

Model	BMC_{10}[a] (mg/kg/day)	$BMCL_{10}$[a] (mg/kg/day)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose near BMC	Dose near control
Dichotomous Hill			NA	38.94	-4.04×10^{-4}	-4.04×10^{-4}
Gamma[d]	5.28	3.45	0.67	35.64	-3.92×10^{-4}	-3.92×10^{-4}
Log-Logistic[e]			0.99	34.95	-3.90×10^{-4}	-3.90×10^{-4}
Log-Probit[e]	8.31	5.32	0.74	35.44	0.405	-3.90×10^{-4}
Multistage (3-degree)[f]	5.28	3.45	0.85	33.64	-3.90×10^{-4}	-3.90×10^{-4}
Multistage (2-degree)[f]	5.28	3.45	0.85	33.64	-3.90×10^{-4}	-3.90×10^{-4}
Multistage (1-degree)[f,g]	**5.28**	**3.45**	**0.85**	**33.64**	**-3.90×10^{-4}**	**-3.90×10^{-4}**
Weibull[d]	5.28	3.45	0.67	35.64	-8.25×10^{-3}	-8.25×10^{-3}
Logistic			0.09	41.09	0.366	-0.142
Probit			0.08	41.47	0.361	-0.145

[a]BMC and BMCL values for models that do not provide adequate fit are not included in the table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at concentrations immediately below and above the BMC.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]Selected model. All models except the LogLogistic, Logistic, Probit, and dichotomous Hill models provided adequate fit to the data (the Weibull and 2- and 3-degree Multistage 2- and 3-degree models converged onto the 1-degree Multistage model). BMCLs for models providing adequate fit were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (1-Degree Multistage).

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

For nasal lesions in male and female rats (combined), seven frequentist, restricted models provided adequate fit to the data. BMCLs for models providing adequate fit were not sufficiently close (differed by 3-fold), so the lowest BMCL was selected (Log-Logistic). The Log-Logistic model estimated a BMC_{10} and $BMCL_{10}$ of 6.78 and 2.38 ppm, respectively. The results of the BMD modeling are summarized in Table A-6.

Table A-6. Model Predictions for Incidence of Nasal Respiratory Epithelium Hyperplasia in Male and Female F344 Rats exposed to 1,2-Dichloropropane for 13 Weeks (Nitschke et al. 1988)

Model	BMC_{10}[a] (mg/kg/day)	$BMDC_{10}$[a] (mg/kg/day)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose near BMC	Dose near control
Dichotomous Hill			0.70	67.98	-5.52×10^{-4}	-5.52×10^{-4}
Gamma[d]	6.10	4.48	0.84	66.16	-5.57×10^{-4}	-5.57×10^{-4}
Log-Logistic[e,f]	**6.76**	**2.38**	**0.70**	**67.98**	**-5.52×10^{-4}**	**-5.52×10^{-4}**
Log-Probit[e]	9.80	7.17	0.84	64.62	0.737	-5.52×10^{-4}
Multistage (3-degree)[g]	6.10	4.48	0.95	64.16	-5.52×10^{-4}	-5.52×10^{-4}
Multistage (2-degree)[g]	6.10	4.48	0.95	64.16	-5.52×10^{-4}	-5.52×10^{-4}
Multistage (1-degree)[g]	6.10	4.48	0.84	66.16	-5.52×10^{-4}	-5.52×10^{-4}
Weibull[d]	6.10	4.48	0.95	64.16	-5.52×10^{-4}	-5.52×10^{-4}
Logistic			0.04	74.98	0.550	-1.82
Probit			0.03	75.27	0.565	-1.82

[a]BMC and BMCL values for models that do not provide adequate fit are not included in the table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at concentrations immediately below and above the BMC.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Selected model. All models except the Logistic, Probit, and dichotomous Hill models provided adequate fit to the data. BMCLs for remaining models providing adequate fit were not sufficiently close (differed by ≥3-fold), so the model with the lowest BMCL was selected (Log-Logistic).
[g]Betas restricted to ≥0.

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

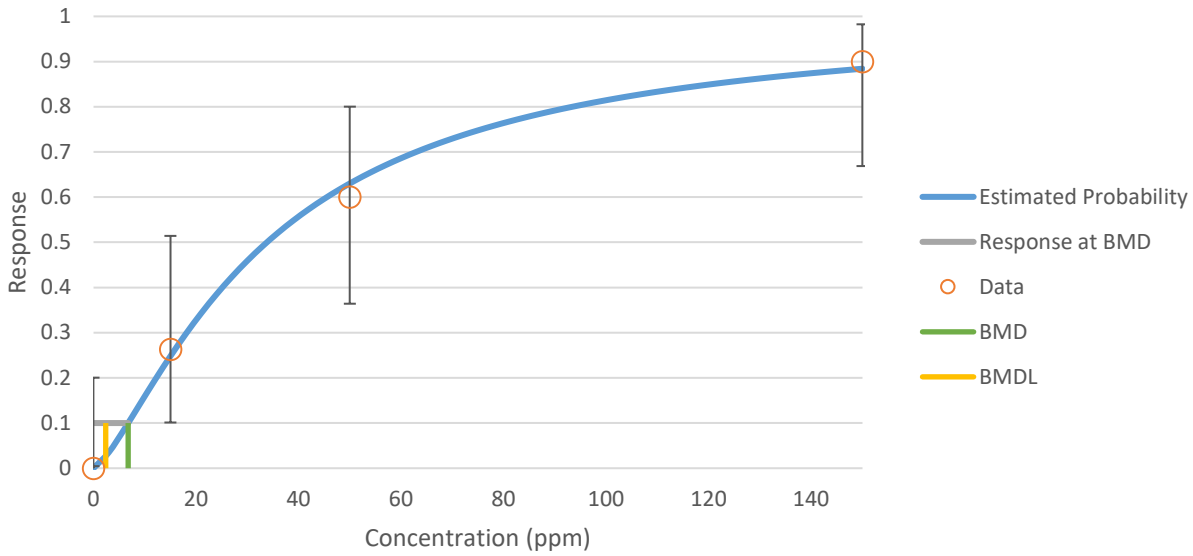
Table A-7 summarizes the potential candidate PODs for the intermediate-duration inhalation MRL for 1,2-dichloropropane. While the female data have the lowest BMC, the BMCL of 2.38 ppm from the combined male and female data was selected as the POD for the MRL derivation because it has the highest statistical power. The Log-Logistic model fit to the nasal respiratory epithelium hyperplasia in the male and female rats presented in Figure A-1.

Table A-7. Candidate Points of Departure 1,2-Dichloropropane Intermediate-Duration Inhalation MRL

Endpoint	BMC_{10} (ppm)	$BMCL_{10}$ (ppm)
Increased incidence of nasal lesions in males	9.08	2.44
Increased incidence of nasal lesions in females	5.28	3.45
Increased incidence of nasal lesions in males and females (combined)	6.76	2.38

BMC = benchmark concentration; BMCL = 95% lower confidence limit on the BMC; MRL = Minimal Risk Level

Figure A-1. Fit of Log-Logistic Model to Data for Combined Incidence of Nasal Respiratory Epithelium Hyperplasia in Male and Female F344 Rats Exposed to 1,2-Dichloropropane for 13 Weeks



Adjustment for Intermittent Exposure: The $BMCL_{10}$ of 2.38 ppm was adjusted from intermittent exposure to account for a continuous exposure scenario:

$BMCL_{ADJ}$ = 2.38 ppm x (6 hours/24 hours) x (5 days/7 days) = 0.43 ppm

Human Equivalent Concentration: A human equivalent concentration (HEC) was calculated by multiplying the duration-adjusted BMCL by the regional gas dose ratio (RGDR) for the extrathoracic region of the respiratory tract. The $RGDR_{ET}$ of 0.115 was calculated using the following equation:

$$RGDR_{ET} = (V_E/SA_{ET})_A/(V_E/SA_{ET})_H$$

where:

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

V_E = 119 mL/minute and SA_{ET} = 15 cm^2 in rats and V_E = 13,800 mL/minute and SA_{ET} = 200 cm^2 in humans (EPA 1994).

$RGDR_{ET}$ = (119 mL/minute ÷ 15 cm^2)/(13,800 mL/minute ÷ 200 cm^2) = 0.115

$BMCL_{HEC} = BMCL_{ADJ}$ x $RGDR_{ET}$
$BMCL_{HEC}$ = 0.43 ppm x 0.115 = 0.05 ppm

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

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

MRL = $BMCL_{10[HEC]}$ ÷ UFs
MRL = 0.05 ppm ÷ (3 x 10) = 0.002 ppm

Other Additional Studies or Pertinent Information that Lend Support to this MRL: The upper respiratory tract is the most sensitive target following both acute- and intermediate-duration inhalation exposure, and the rat is the most sensitive species tested. As discussed in the acute-duration inhalation MRL worksheet, olfactory mucosal degeneration was observed in rats and mice exposed to ≥100 ppm and rabbits at 1,000 ppm for 2 weeks (Nitschke and Johnson 1983). In intermediate-duration studies, nasal cavity lesions were observed in rats exposed to ≥15 ppm (lowest concentration tested), including hyperplasia of the respiratory epithelium at ≥15 ppm, degeneration of the olfactory epithelium at ≥50 ppm, atrophy of the olfactory epithelium at ≥125 ppm, submucosal inflammation at ≥150 ppm, and inflammation of the respiratory epithelium at ≥1,000 ppm (Nitschke et al. 1988; Umeda et al. 2010). Intermediate-duration studies also observed nasal lesions in mice at ≥300 ppm (but not ≤200 ppm) (Matsumoto et al. 2013; Nitschke et al. 1988) and rabbits at 1,000 ppm (but not ≤500 ppm) (Nitschke et al. 1988). In chronic studies, nasal lesions were observed in rats at ≥80 ppm (lowest concentration tested), including atrophy of olfactory epithelium, inflammation of the respiratory epithelium, squamous cell metaplasia of respiratory epithelium, hyperplasia of the transitional epithelium, squamous cell hyperplasia, and hyperplasia of the submucosal glands (Umeda et al. 2010) and mice at ≥80 ppm (but not 32 ppm), including atrophy of olfactory epithelium and metaplasia of the olfactory epithelium and submucosal glands (Matsumoto et al. 2013).

Limited evidence from accident reports following chemical spills suggest that inhalation exposure to 1,2-dichloropropane causes respiratory irritation in humans following acute exposure to presumably high concentrations (exposure levels not available) (ACGIH 2014; Rubin 1988).

Agency Contacts (Chemical Managers): Carolyn Harper

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2-Dichloropropane
CAS Numbers: 78-87-5
Date: November 2021
Profile Status: Final
Route: Inhalation
Duration: Chronic

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

Rationale for Not Deriving an MRL: A chronic-duration inhalation MRL was not derived due to lack of adequate low-concentration data for the critical effect. As a result, there is too much uncertainty in the chronic database to support derivation of an MRL based on chronic data. It is not considered appropriate to use the intermediate-duration data for derivation of a chronic MRL because there is evidence that the severity of nasal lesions increases with longer durations of exposure. Therefore, we cannot be sure that the intermediate MRL would be protective for chronic exposure. Two chronic-duration inhalation studies evaluating comprehensive endpoints in rats and mice are available (Matsumoto et al. 2013; Umeda et al. 2010); the results of these studies are summarized in Table A-8. The most sensitive effect identified in rats was nasal lesions at ≥80 ppm (lowest concentration tested); the lesions included atrophy of the olfactory epithelium, inflammation and squamous cell metaplasia of respiratory epithelium, and hyperplasia of the transitional epithelium (Umeda et al. 2010). In mice, the most sensitive effect was basophilic changes and cortical mineralization in the kidney of male mice at ≥32 ppm (lowest concentration tested) and atrophy of the olfactory epithelium at ≥80 ppm (Matsumoto et al. 2013). While the LOAEL identified for renal effects was lower than the LOAEL identified for nasal lesions, renal effects were not selected as critical effects because there is a lack of consistent evidence for renal effects in exposed animals and the systematic review of renal toxicity determined that data are inadequate to determine if kidney toxicity will be observed in humans exposed to 1,2-dichloropropane. Therefore, the lowest LOAEL for the critical effect of nasal lesions was 80 ppm. This LOAEL is >5-fold higher than the LOAEL observed for nasal lesions following intermediate-duration exposure (15 ppm; Nitschke et al. 1988). Therefore, available chronic studies are inadequate to characterize low-concentration effects of chronic 1,2-dichloropropane inhalation exposure.

Table A-8. Summary of Candidate Critical Effects for Chronic Inhalation MRL for 1,2-Dichloropropane

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Respiratory effects					
F344 rat	104 weeks (6 hours/day, 5 days/week)	ND	80	Atrophy of olfactory epithelium, inflammation and squamous cell metaplasia of respiratory epithelium, and hyperplasia of the transitional epithelium	Umeda et al. 2010
B6D2F1/Crlj mouse	104 weeks (6 hours/day, 5 days/week)	32	80	Atrophy of olfactory epithelium	Matsumoto et al. 2013

Table A-8. Summary of Candidate Critical Effects for Chronic Inhalation MRL for 1,2-Dichloropropane

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Renal effects					
B6D2F1/Crlj mouse	104 weeks (6 hours/day, 5 days/week)	ND	32	Basophilic changes and cortical mineralization in kidney; males only	Matsumoto et al. 2013

LOAEL = lowest observed adverse effect level; MRL = Minimal Risk Level; ND = not determined; NOAEL = no-observed-adverse-effect level

Agency Contacts (Chemical Managers): Carolyn Harper

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2-Dichloropropane
CAS Numbers: 78-87-5
Date: November 2021
Profile Status: Final
Route: Oral
Duration: Acute
MRL 0.3 mg/kg/day
Critical Effect: Maternal anemia
Reference: Berdasco et al. 1988 and Kirk et al. 1995
Point of Departure: $BMDL_{1SD}$ of 30 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 17, 18
Species: Rabbit

MRL Summary: An acute-duration oral MRL of 0.3 mg/kg/day was derived for 1,2-dichloropropane based on evidence of maternal anemia in rabbits exposed to doses ≥100 mg/kg/day on gestation days 7–19 (Berdasco et al. 1988; Kirk et al. 1995). The MRL is based on the $BMDL_{1SD}$ of 30 mg/kg/day for increased maternal reticulocyte counts relative to control animals and a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Selection of the Critical Effect: Several studies have evaluated the toxicity of 1,2-dichloropropane following acute-duration oral exposure. The most sensitive effects identified in acute oral studies included hematological, developmental, neurological, and body weight effects; see Table A-9. Since all of these adverse effects occurred at similar doses, all were considered for MRL derivation.

Table A-9. Summary of Candidate Critical Effects for Acute Oral MRL for 1,2-Dichloropropane

Species	Duration/route	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Hematological effects					
New Zealand rabbit	GDs 7–19 (GO)	25	100	Maternal anemia	Berdasco et al. 1988
New Zealand rabbit	GDs 7–19 (GO)	50	150	Maternal anemia	Kirk et al. 1995
Developmental effects					
Sprague-Dawley rat	GDs 6–15 (GO)	30	125	Delayed skull ossification	Kirk et al. 1995
New Zealand rabbit	GDs 7–19 (GO)	50	150	Delayed skull ossification	Kirk et al. 1995
Neurological effects					
Sprague-Dawley rat	1–10 days (GO)	ND	100	CNS depression	Bruckner et al. 1989
Sprague-Dawley rat	GDs 6–15 (GO)	30	125	Clinical signs of neurotoxicity in dams	Kirk et al. 1995
Wistar rat	Once (G)	ND	145	CNS depression	Shell Oil Co.1982

Table A-9. Summary of Candidate Critical Effects for Acute Oral MRL for 1,2-Dichloropropane

Species	Duration/route	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Body weight effects					
Sprague-Dawley rat	GDs 6–15 (GO)	30	125	Decreased maternal body weight gain	Kirk et al. 1995

CNS = central nervous system; G = gavage (no vehicle); GD = gestation day; GO = gavage (oil vehicle); LOAEL = lowest observed adverse effect level; MRL = Minimal Risk Level; NOAEL = no-observed-adverse-effect level; ND = not determined

In order to identify the most sensitive endpoint, BMD modeling was attempted for candidate critical endpoints in Table A-9 when data were amenable to modeling. Data modeled included maternal anemia in rabbits, delayed ossification in rabbits and rats, and decreased maternal body weight gain in rats (see Tables A-10, A-11, and A-12); data for neurological effects were not adequate for modeling due to qualitative and/or incomplete quantitative reporting. The data were fit to all available dichotomous or continuous models in EPA's BMDS (version 3.1.2) using a BMR of 1 standard deviation (hematological data), 10% relative deviation (body weight data), or 5% extra risk (developmental endpoints). Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, BMDL that is not 10 times lower than the lowest non-zero dose, and scaled residual within ±2 units at the data point (except the control) closest to the predefined BMR. Among all of the models providing adequate fit to the data, the lowest BMDL (95% lower confidence limit on the BMD) 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.

Table A-10. Maternal Anemia in New Zealand Rabbits Following Gavage Administration of 1,2-Dichloropropane on GDs 7–19

	Dose (mg/kg/day)			
	0	25	100	250
Maternal reticulocyte counts Mean ± SD (N)	2.1±1.2 (4)	2.5±0.4 (3)	4.5±1 (5)	7.8±1.5 (3)

GD = gestation day; N = number; SD = standard deviation

Source: Berdasco et al. 1988

Table A-11. Maternal Anemia and Incidence of Delayed Ossification in New Zealand Rabbits Following Gavage Administration of 1,2-Dichloropropane on GDs 7–19

	Dose (mg/kg/day)			
	0	15	50	150
Maternal reticulocyte counts Mean ± SD (N)	3.2±0.6 (18)	3.6±0.7 (16)	3.8±0.9 (17)	6.7±1.7 (15)
Delayed ossification Litter incidence (% incidence)	0/18 (0%)	0/16 (0%)	2/17 (12%)	6/15 (40%)

GD = gestation day; N = number; SD = standard deviation

Source: Kirk et al. 1995

Table A-12. Maternal Body Weight Gain and Incidence of Delayed Ossification in Sprague-Dawley Rats Following Gavage Administration of 1,2-Dichloropropane on GDs 6–15

	Dose (mg/kg/day)			
	0	10	30	125
Maternal body weight gain (g) Mean ± SD (N)	189.2±30 (25)	188.8±23.7 (28)	188.7±23.5 (28)	170.5±23.7 (30)
Delayed ossification Litter incidence (% incidence)	8/25 (32%)	8/28 (29%)	10/28 (36%)	16/30 (53%)

GD = gestation day; N = number; SD = standard deviation

Source: Kirk et al. 1995

Suitable models were not identified for delayed ossification data in rabbits or rats (Kirk et al. 1995). Models produced questionable results, providing BMDL values that were inconsistent with empirical data (values of 5.6 and 10 mg/kg/day, respectively, were substantially lower than two no-effect dose levels in both studies). Therefore, ATSDR used the NOAEL/LOAEL approach for this endpoint.

For maternal anemia in rabbits reported by Berdasco et al. (1998), seven frequentist, constant variance models provided adequate fit to the data. BMDLs for models providing adequate fit were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Linear). The unrestricted Linear model estimated a BMD_{1SD} and $BMDL_{1SD}$ of 41 and 30 mg/kg/day, respectively. The results of the BMD modeling are summarized in Table A-13.

Table A-13. Model Predictions (Constant Variance) for Maternal Reticulocyte Count in Pregnant New Zealand White Rabbits Orally Administered 1,2-Dichloropropane on GDs 7–19 (Berdasco et al. 1988)

Model	BMD_{1SD}[a] (mg/kg/day)	$BMDL_{1SD}$[a] (mg/kg/day)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose near BMD	Dose near control
Exponential (model 2)[d]	74	57	0.29	49.09	1.16	-0.78
Exponential (model 3)[d]	74	57	0.29	49.09	1.16	-0.78
Exponential (model 4)[d]	38	22	0.74	48.69	-0.28	0.16
Exponential (model 5)[d]			NA	50.58	0.00	0.00
Hill[d]			NA	50.58	0.00	0.00
Polynomial (3-degree)[e]	41	30	0.92	46.75	-0.29	0.05
Polynomial (2-degree)[e]	41	30	0.92	46.75	-0.29	0.05
Power[d]	41	30	0.92	46.75	-0.29	0.05
Linear[e,f]	**41**	**30**	**0.92**	**46.75**	**-0.29**	**0.05**

[a]BMD and BMDL values for models that do not provide adequate fit are not included in the table.
[b]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at concentrations immediately below and above the BMC.
[d]Power restricted to ≥1.
[e] Coefficients restricted to be positive.
[f]Selected model. Constant variance models provided adequate fit to the variance data. With constant variance model applied, all models except the Exponential 5 and the Hill models provided adequate fit to the means (the Exponential 3 model converged on Exponential model 2, and Power and Polynomial models all converged upon the Linear model). BMDLs for models providing adequate fit were sufficiently close (differed by <3-fold), so the model with the lowest AIC is selected (Linear model)

AIC = Akaike Information Criterion; BMD = benchmark dose (maximum likelihood estimate of the concentration associated with the selected benchmark response); $BMDL_{1SD}$ = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., 1SD = exposure dose associated with a 1 standard deviation change in outcome); GD = gestation day; NA = not applicable (goodness of fit test cannot be calculated)

For maternal anemia in rabbits reported by Kirk et al. (1995), six frequentist, non-constant variance models provided adequate fit to the data. BMDLs for models providing adequate fit were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Exponential 2). The restricted Exponential 2 model estimated a BMD_{1SD} and $BMDL_{1SD}$ of 37 and 30 mg/kg/day, respectively. The results of the BMD modeling are summarized in Table A-14.

Table A-14. Model Predictions (Non-constant Variance) for Maternal Reticulocyte Count in Pregnant New Zealand White Rabbits Orally Administered 1,2-Dichloropropane on GDs 7–19 (Kirk et al. 1995)

Model	BMD_{1SD}[a] (mg/kg/day)	$BMDL_{1SD}$[a] (mg/kg/day)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose near BMD	Dose near control
Exponential (model 2)[d,e]	**37**	**30**	**0.35**	**176.44**	**-1.25**	**-0.04**
Exponential (model 3)[d]	47	30	0.19	178.05	-0.76	-0.43
Exponential (model 4)[d]			0.04	180.61	0.71	0.21
Exponential (model 5)[d]			NA	180.48	-0.69	-0.60

Table A-14. Model Predictions (Non-constant Variance) for Maternal Reticulocyte Count in Pregnant New Zealand White Rabbits Orally Administered 1,2-Dichloropropane on GDs 7–19 (Kirk et al. 1995)

Model	BMD_{1SD}[a] (mg/kg/day)	$BMDL_{1SD}$[a] (mg/kg/day)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose near BMD	Dose near control
Hill[d]			NA	180.50	-0.74	-0.57
Polynomial (3-degree)[f]	49	27	0.28	177.52	-0.57	-0.41
Polynomial (2-degree)[f]	48	27	0.21	177.93	-0.71	-0.44
Power[d]	50	25	0.14	178.48	-0.69	-0.60
Linear[f]	29	22	0.12	178.60	0.71	0.23

[a]BMD and BMDL values for models that do not provide adequate fit are not included in the table.
[b]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at concentrations immediately below and above the BMC.
[d]Power restricted to ≥1.
[e]Selected model. Constant variance model did not fit the variance data, but non-constant variance model did. With nonconstant variance model applied, all models except for Exponential models 4 and 5, and the Hill model, provided adequate fit to means. BMDLs for models providing adequate fit were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Exponential model 2).
[f]Coefficients restricted to be positive.

AIC = Akaike Information Criterion; BMD = benchmark dose (maximum likelihood estimate of the concentration associated with the selected benchmark response); $BMDL_{1SD}$ = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., 1SD = exposure dose associated with a 1 standard deviation change in outcome); GD = gestation day; NA = not applicable (goodness of fit test cannot be calculated)

For decreased maternal body weight gain reported by Kirk et al. (1995), seven frequentist, non-constant variance models provided adequate fit to the data. BMDLs for models providing adequate fit were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (2-degree Polynomial). The restricted 2-degree Polynomial model estimated a BMD_{RD10} and $BMDL_{RD10}$ of 126 and 84 mg/kg/day, respectively. The results of the BMD modeling are summarized in Table A-15.

Table A-15. Model Predictions (Constant Variance) for Reduced Body Weight Gain in Female Sprague-Dawley Rats Orally Administered 1,2-Dichloropropane on GDs 6–15 (Kirk et al. 1995)

Model	BMD_{RD10}[a] (mg/kg/day)	$BMDL_{RD10}$[a] (mg/kg/day)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose near BMD	Dose near control
Exponential (model 2)[d]	120	80	0.78	1,033.8	-0.14	-0.35
Exponential (model 3)[d]	126	83	0.95	1,035.3	0.00	0.03
Exponential (model 4)[d]	120	80	0.78	1,033.8	-0.14	-0.35
Exponential (model 5)[d]			NA	1,037.3	0.00	0.04
Hill[d]			NA	1,037.3	-9,999.00	0.04
Polynomial (3-degree)[e]	126	85	0.95	1,035.3	0.00	0.02
Polynomial (2-degree)[e,f]	**126**	**84**	**0.99**	**1,033.3**	**-0.01**	**-0.02**

Table A-15. Model Predictions (Constant Variance) for Reduced Body Weight Gain in Female Sprague-Dawley Rats Orally Administered 1,2-Dichloropropane on GDs 6–15 (Kirk et al. 1995)

Model	BMD_{RD10}[a] (mg/kg/day)	$BMDL_{RD10}$[a] (mg/kg/day)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose near BMD	Dose near control
Power[d]	126	85	0.95	1,035.3	0.00	0.03
Linear[e]	120	82	0.80	1,033.8	-0.12	-0.34

[a]BMD and BMDL values for models that do not provide adequate fit are not included in the table.
[b]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at concentrations immediately below and above the BMC.
[d]Power restricted to ≥1.
[e]Coefficients restricted to be positive.
[f]Selected model. Constant variance models provided adequate fit to the variance data. With constant variance model applied, all models provided adequate fit to the means, except for the Hill and Exponential 5 models. BMDLs for models providing adequate fit were sufficiently close (differed by <3-fold), so the model with the lowest AIC is selected (2-degree Polynomial).

AIC = Akaike Information Criterion; BMD = benchmark dose (maximum likelihood estimate of the concentration associated with the selected benchmark response); $BMDL_{RD10}$ = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., RD10 = exposure dose associated with a 10% change in outcome); GD = gestation day; NA = not applicable (goodness of fit test cannot be calculated)

Table A-16 summarized the potential candidate PODs for the acute-duration oral MRL for 1,2-dichloropropane. The lowest BMD value of 37 mg/kg/day is based on maternal anemia in rabbits (Kirk et al. 1995); this value is lower than BMD/LOAEL values associated with developmental, neurological, or body weight effects. Maternal anemia reported in the Kirk et al. (1995) and Berdasco et al. (1988) studies and delayed skull ossification in rats (Kirk et al. 1995) provided the same POD based on BMDL or NOAEL values, respectively (30 mg/kg/day). Based on adequate BMD modeling and consistency of results from two studies, maternal anemia was selected as the critical effect. For the Kirk et al. (1995) study, the Exponential 2 model fit to the hematological data in maternal rabbits is presented in Figure A-3. For the Berdasco et al. (1998) study, the Linear model fit to the hematological data in maternal rabbits is presented in Figure A-2; the 2- and 3-Degree Polynomial and Power models converge on the Linear model.

Table A-16. Candidate Points of Departure for 1,2-Dichloropropane Acute-Duration Oral MRL

Endpoint	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	BMD (mg/kg/day)	BMDL (mg/kg/day)
Maternal anemia (Kirk et al. 1995)			37	30
Maternal anemia (Berdasco et al. 1988)			41	30
Delayed skull ossification (rat)	30	125		
Delayed skull ossification (rabbit)	50	150		
CNS depression (Sprague-Dawley rat)	ND	100		
Clinical signs of neurotoxicity	30	125		
CNS depression (Wistar rat)	ND	145		
Decreased maternal body weight gain			126	84

BMD = benchmark dose; BMDL = 95% lower confidence limit on the BMD; CNS = central nervous system; LOAEL = lowest-observed-adverse-effect level; MRL = Minimal Risk Level; ND = not determined; NOAEL = no-observed-adverse-effect level

Figure A-2. Fit of Exponential Model 2 to Data for Maternal Reticulocyte Count in Pregnant New Zealand White Rabbits Orally Administered 1,2-Dichloropropane on Gestational Days 7–19 (Kirk et al. 1995)

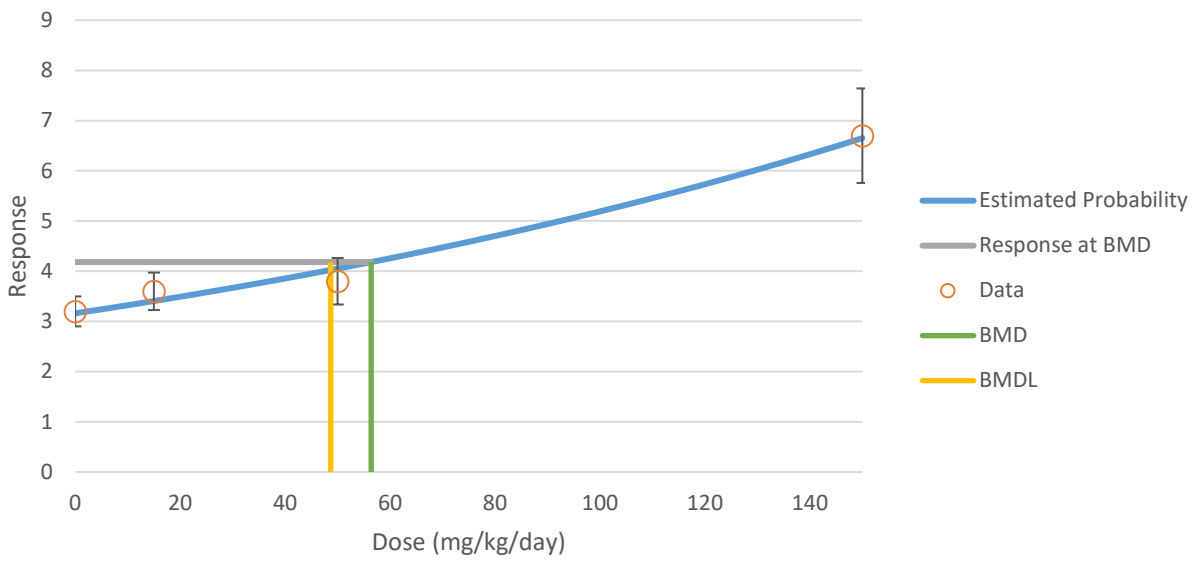
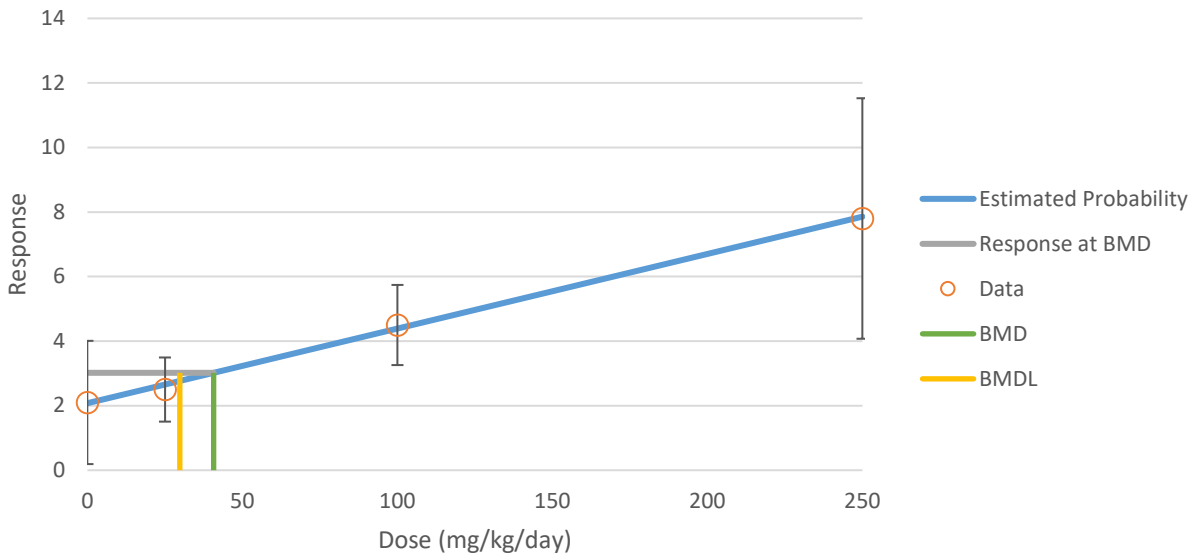


Figure A-3. Fit of Linear Model to Data for Maternal Reticulocyte Count in Pregnant New Zealand White Rabbits Orally Administered 1,2-Dichloropropane on Gestational Days 7–19 (Berdasco et al. 1988)



Selection of the Principal Study: The two studies that provided identical BMCL values for the critical effect of maternal anemia were selected as co-principal studies for derivation of the acute oral MRL (Berdasco et al. 1988; Kirk et al. 1995).

Summary of the Co-Principal Studies:

Berdasco NM, Johnson KA, Hanley TRJ. 1988. Propylene dichloride: Oral teratology probe study in New Zealand white rabbits with cover letter dated 100188. Submitted to the U.S. Environmental Protection Agency under TSCA Section 4. OTS0516583. 86890000004.

Kirk HD, Berdasco NM, Breslin WJ, et al. 1995. Developmental toxicity of 1,2-dichloropropane (PDC) in rats and rabbits following oral gavage. Fundam Appl Toxicol 28(1):18-26.

Berdasco et al. (1988) administered 1,2-dichloroporpane (99.9% pure) to groups of artificially-inseminated rabbits via gavage in corn oil at doses of 0, 25, 100, or 250 mg/kg/day on GDs 7–19. Does were sacrificed on GD 20. Maternal toxicity endpoints evaluated included mortality, clinical signs of toxicity, body weight, gross necropsy, hematology (on GD 20), organ weights (kidney, liver, spleen), and eye examination (*in situ*, glass slide technique). Reproductive endpoints included the number of corpora lutea and numbers and positions of implantations and resorptions.

In the high-dose group, 2/7 does died; the cause of death was undetermined. Two additional high-dose animals showed weight loss and complete litter loss. Overall body weights did not differ between control and exposed animals and the resorption rates were not significantly different between groups. There were no exposure-related changes in organ weights or gross necropsy. Several changes were observed in hematological parameters, indicating regenerative anemia, including: 22–24% decreases in erythrocyte count, hemoglobin, and hematocrit at 500 mg/kg/day; a 2–3.7-fold increase in the percentage of reticulocytes at ≥100 mg/kg/day; increased slight-to-moderate polychromasia in red blood cells at ≥100 mg/kg/day; and increased slight-to-moderate anisocytosis in red blood cells at 250 mg/kg/day.

Kirk et al. (1995) administered 1,2-dichloropropane (99.9% pure) to groups of artificially inseminated rabbits via gavage in corn oil at doses of 0, 15, 50, or 150 mg/kg/day on GDs 7–19 (18 rabbits/group). Does were sacrificed on GD 28. Maternal toxicity endpoints evaluated included mortality, clinical signs, body weight, hematology (on GD 19), and organ weights (liver, kidney, spleen, gravid uterus). Reproductive and developmental endpoints included number of corpora lutea, number and position of implantations, resorptions, and live or dead fetuses, sex and body weight of each fetus, and external, visceral, and skeletal malformations.

In the high-dose group, 2/18 does died (one due to intubation error; cause of death not reported in second doe). Intermittent anorexia was observed in 17/18 does in the high-dose group during dosing. Significantly lowered weight gains were observed in high dose rabbits during dosing (GDs 7–20), but no significant differences were observed in absolute body weight compared to controls. Evidence of regenerative anemia was observed at the high dose (decreased erythrocyte counts, hemoglobin concentration, and hematocrit and increased platelet, leukocyte, and reticulocyte counts; slight-to-moderate anisocytosis, poikilocytosis, and/or polychromasia of red blood cells observed microscopically). No organ weight changes were observed. No exposure-related changes in the number of litters or pregnancy outcomes were observed. The litter incidence of delayed ossification of the skull was significantly elevated at 150 mg/kg/day (6/15 litters, 6/140 fetuses) and non-significantly elevated at 50 mg/kg/day (2/17 litters, 2/142 fetuses), compared with controls (0/18 litters, 0/149 fetuses).

Selection of the Point of Departure for the MRL: The $BMDL_{1SD}$ of 30 mg/kg/day for increased maternal reticulocyte counts (from both studies) was selected as the POD.

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

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

$MRL = BMDL_{1SD} \div UFs$
$MRL = 30 \text{ mg/kg/day} \div (10 \times 10) = 0.3 \text{ mg/kg/day}$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: As detailed in Appendix C, hematological effects are a presumed health effect for humans. Several human case studies reported hematological effects, including hemolytic anemia, following accidental or intentional oral exposure to high levels of 1,2-dichloropropane (Di Nucci et al. 1988; Fiaccadori et al. 2003; Lucantoni et al. 1991, 1992; Perbellini et al. 1985; Pozzi et al. 1985). In addition to the findings in maternal rabbits by Berdasco et al. (1988) and Kirk et al. (1995) following acute exposure, hemolytic anemia has also been reported following oral exposure in rats at an acute dose of 2,000 mg/kg/day (Imberti et al. 1990) and intermediate-duration doses as low as 100 mg/kg/day (Bruckner et al. 1989; Kirk et al. 1990). Evidence of hemolytic anemia was also observed in rats, mice, and rabbits following intermediate-duration inhalation exposure to concentrations as low as 150 ppm (Matsumoto et al. 2013; Nitschke et al. 1988; Umeda et al. 2010).

Agency Contacts (Chemical Managers): Carolyn Harper

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2-Dichloropropane
CAS Numbers: 78-87-5
Date: November 2021
Profile Status: Final
Route: Oral
Duration: Intermediate
MRL 0.07 mg/kg/day
Critical Effect: Hemolytic anemia
Reference: Bruckner et al. 1989
Point of Departure: LOAEL of 100 mg/kg/day ($LOAEL_{ADJ}$ of 71 mg/kg/day)
Uncertainty Factor: 1,000
LSE Graph Key: 19
Species: Rabbit

MRL Summary: An intermediate-duration oral MRL of 0.07 mg/kg/day was derived for 1,2-dichloropropane based on evidence of hemolytic anemia in rats exposed to doses ≥100 mg/kg/day for 13 weeks (5 days/week) (Bruckner et al. 1989). The MRL is based on the LOAEL of 100 mg/kg/day, which was adjusted to a continuous exposure ($LOAEL_{ADJ}$) of 71 mg/kg/day for increased serum bilirubin, hemosiderosis in the spleen, and erythropoietic hyperplasia and a total uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

Selection of the Critical Effect: Several studies have evaluated the toxicity of 1,2-dichloropropane following intermediate-duration oral exposure. The most sensitive effects identified in intermediate oral studies included hematological, hepatic, and body weight effects; see Table A-17. Since all of these adverse effects occurred at similar doses, all were considered for MRL derivation.

Table A-17. Summary of Candidate Critical Effects for Intermediate Oral MRL for 1,2-Dichloropropane

Species	Duration/route	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Hepatic effects					
B6C3F1 mouse	4 weeks 5 days/week (GO)	ND	125	Increased absolute liver weight	Gi et al. 2015a
B6C3F1 mouse	4 weeks 5 days/week (GO)	ND	125	Increased relative liver weight	Gi et al. 2015a
B6C3F1 mouse	4 weeks 5 days/week (GO)	ND	125	Mild fatty change	Gi et al. 2015a
Body weight effects					
F344 rat	13 weeks 5 days/week (GO)	65	200	Decreased body weight in males	Johnson and Gorzinski 1988

Table A-17. Summary of Candidate Critical Effects for Intermediate Oral MRL for 1,2-Dichloropropane

Species	Duration/route	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Hematological effects					
Sprague-Dawley rat	13 weeks 5 days/week (GO)	ND	100	Hemolytic anemia	Bruckner et al. 1989

GO = gavage (oil vehicle); LOAEL = lowest observed adverse effect level; MRL = Minimal Risk Level; ND = not determined; NOAEL = no-observed-adverse-effect level

In order to identify the most sensitive endpoint, BMD modeling was attempted for candidate critical endpoints listed in Table A-17 when data were amenable to modeling. Data modeled included increased absolute and relative liver weight in mice and decreased body weight in rats (see Tables A-18 and A-19). The data were fit to all available continuous models in EPA's BMDS (version 3.1.2) using a BMR of 10% relative deviation. Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, BMDL that is not 10 times lower than the lowest non-zero dose, and scaled residual within ±2 units at the data point (except the control) closest to the predefined BMR. Among all of the models providing adequate fit to the data, the lowest BMDL (95% lower confidence limit on the BMD) 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. Histological effects in the liver were not amenable for modeling because the incidence increased from 0% in controls to 100% in the lowest dose tested (Gi et al. 2015a). Hematological data for rats were inadequate for modeling because exact animal number per group was not reported (Bruckner et al. 1989). Therefore, a NOAEL/LOAEL approach was used for these studies.

Table A-18. Body Weight in Male F344 Rats Following Gavage Administration of 1,2-Dichloropropane for 13 Weeks

	Dose (mg/kg/day)			
	0	20	65	200
Terminal body weight; mean±SD (N)	341.7±11.2 (15)	334.9±13.7 (15)	331.0±25.7 (15)	308.0±14.8 (15)

N = number; SD = standard deviation

Source: Johnson and Grozinski 1988

Table A-19. Liver Weight in B6C3F1 Mice Following Gavage Administration of 1,2-Dichloropropane for 4 Weeks (Gi et al. 2015a)

	Dose (mg/kg/day)		
	0	125	250
Absolute liver weight; mean±SD (N)	0.93±0.05 (5)	1.04±0.03 (5)	1.09±0.06 (5)
Relative liver weight; mean±SD (N)	3.67±0.16 (5)	4.03±0.20 (5)	4.2±0.14 (5)

N = number; SD = standard deviation

Source: Gi et al. 2015a

None of the BMD models (with constant variance or nonconstant variance) provided adequate fit to the decreased body weight in male rats. Therefore, a NOAEL/LOAEL approach was used for this endpoint.

For absolute liver weight, five frequentist, constant variance models provided adequate fit to the data. BMDLs for models providing adequate fit were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Linear); the 2-Degree Polynomial and Power models converged on the Linear model. The unrestricted Linear model estimated a BMD_{RD10} and $BMDL_{RD10}$ of 147 and 109 ppm, respectively. The results of the BMD modeling are summarized in Table A-20.

Table A-20. Model Predictions (Constant Variance) for Absolute Liver Weight in Male B6C3F1 Mice Orally Administered 1,2-Dichloropropane 5 Days/Week for 5 Weeks (Gi et al. 2015a)

Model	BMD_{RD10}[a] (mg/kg/day)	$BMDL_{RD10}$[a] (mg/kg/day)	p-Value[b]	AIC	Scaled residuals[c] Dose near BMD	Scaled residuals[c] Dose near control
Exponential (model 2)[d]	153	117	0.18	-43.85	1.07	-0.58
Exponential (model 3)[d]	153	117	0.18	-43.85	1.07	-0.58
Exponential (model 4)[d]			NA	-43.69	0.00	0.00
Exponential (model 5)[d]			<0.0001	-41.69	0.00	0.00
Hill[d]			<0.0001	-41.69	0.00	0.00
Polynomial (2-degree)[e]	147	109	0.22	-44.16	0.98	-0.49
Power[d]	147	109	0.22	-44.16	0.98	-0.49
Linear[e,f]	**147**	**109**	**0.22**	**-44.16**	**0.98**	**-0.49**

[a]BMD and BMDL values for models that do not provide adequate fit are not included in the table.
[b]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at concentrations immediately below and above the BMC.
[d]Power restricted to ≥1.
[e]Coefficients restricted to be positive.
[f]Selected model. Constant variance models provided adequate fit to the variance data. With constant variance model applied, all models provided adequate fit to the means except for the Hill and Exponential 4 and 5 models (Exponential 3 converged upon Exponential 2 and the power and 2-degree polynomial models converged upon the linear model). BMDLs for models providing adequate fit were sufficiently close (differed by <3-fold), so the model with the lowest AIC is selected (Linear).

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{RD10}$ = exposure concentration associated with a 10% change in outcome); NA = not applicable (Goodness of fit test cannot be calculated); RD = relative deviation

For relative liver weight, five frequentist, constant variance models provided adequate fit to the data. BMDLs for models providing adequate fit were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Linear); the 2-Degree Polynomial and Power models converged on the Linear model. The unrestricted Linear model estimated a BMD_{RD10} and $BMDL_{RD10}$ of 175 and 129 ppm, respectively. The results of the BMD modeling are summarized in Table A-21.

Table A-21. Model Predictions (Constant Variance) for Relative Liver Weight in Male B6C3F1 Mice Orally Administered 1,2-Dichloropropane 5 Days/Week for 5 Weeks (Gi et al. 2015a)

Model	BMD_{RD10}[a] (mg/kg/day)	$BMDL_{RD10}$[a] (mg/kg/day)	p-Value[b]	AIC	Scaled residuals[c] Dose near BMD	Scaled residuals[c] Dose near control
Exponential (model 2)[d]	180	135	0.22	-6.70	0.97	-0.52
Exponential (model 3)[d]	180	135	0.22	-6.70	0.97	-0.52
Exponential (model 4)[d]			NA	-6.20	0.00	0.00
Exponential (model 5)[d]			NA	-6.20	0.00	0.00
Hill[d]			<0.0001	-4.20	0.00	0.00

Table A-21. Model Predictions (Constant Variance) for Relative Liver Weight in Male B6C3F1 Mice Orally Administered 1,2-Dichloropropane 5 Days/Week for 5 Weeks (Gi et al. 2015a)

Model	BMD_{RD10}[a] (mg/kg/day)	$BMDL_{RD10}$[a] (mg/kg/day)	p-Value[b]	Scaled residuals[c]		
				AIC	Dose near BMD	Dose near control
Polynomial (2-degree)[e]	175	129	0.26	-6.93	0.90	-0.45
Power[d]	175	129	0.26	-6.93	0.90	-0.45
Linear[e,f]	**175**	**129**	**0.26**	**-6.93**	**0.90**	**-0.45**

[a]BMD and BMDL values for models that do not provide adequate fit are not included in the table.
[b]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at concentrations immediately below and above the BMC.
[d]Power restricted to ≥1.
[e]Coefficients restricted to be positive.
[f]Selected model. Constant variance model provided adequate fit to the variance data. With constant variance model applied, all models except Exponential 4, provided adequate fit to means (Exponential 3 converged upon Exponential 2 and the power and 2-degree polynomial models converged upon the linear model). BMDLs for models providing adequate fit were sufficiently close (differed by <2–3-fold), so the model with the lowest AIC was selected (Linear).

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{RD10}$ = exposure concentration associated with a 10% change in outcome); NA = not applicable (Goodness of fit test cannot be calculated); RD = relative deviation

Table A-22 summarizes the potential candidate PODs for the intermediate-duration oral MRL for 1,2-dichloropropane. Based on the lowest available PODs, hematological effects (hemolytic anemia) were identified as the critical effect for following intermediate-duration oral exposure to 1,2-dichloropropane.

Table A-22. Candidate Points of Departure 1,2-Dichloropropane Acute-Duration Oral MRL

Endpoint	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	BMD (mg/kg/day)	BMDL (mg/kg/day)
Increased absolute liver weight			145	109
Increased relative liver weight			175	129
Mild fatty liver change	ND	125		
Decreased body weight	65	200		
Hemolytic anemia	ND	100		

BMD = benchmark dose; BMDL = 95% lower confidence limit on the BMD; LOAEL = lowest-observed-adverse-effect level; MRL = Minimal Risk Level; NOAEL = no-observed-adverse-effect level;

Selection of the Principal Study: The study with the lowest identified LOAEL for the critical effect of hemolytic anemia was selected as the principal study (Bruckner et al. 1989).

Summary of the Principal Study:

Bruckner JV, MacKenzie WF, Ramanathan R, et al. 1989. Oral toxicity of 1,2-dichloropropane: Acute, short-term, and long-term studies in rats. Fundam Appl Toxicol 12(4):713-730.

Groups of Sprague-Dawley rats were administered 1,2-dichloropropane (99% pure) via gavage in corn oil at doses of 0, 100, 250, 500, or 750 mg/kg/day for 13 weeks (5 days/week). Endpoints evaluated included mortality, clinical signs, body weight, serum chemistry, urinalysis, liver and kidney weight, and histology (liver, kidneys, lungs, brain, adrenals, spleen, stomach, testis, epididymis).

High mortality was observed in the 750 mg/kg/day group, with ~55% mortality within 10 days. The remaining animals were sacrificed moribund. By the end of the 13-week exposure period, >50% of the rats treated with 500 mg/kg/day had died. Survival was at least 90% in remaining groups. The 500 mg/kg/day group showed pronounced CNS depression, but no brain lesions were observed in any groups. Body weight gain was significantly decreased in a dose-related manner in all treatment groups throughout the study. Liver effects were seen only at 500 mg/kg/day and included periportal vacuolization and active fibroplasia. Evidence of hemolytic anemia was seen at all doses and was dose-related in severity. At 100 mg/kg/day, serum bilirubin was increased, and hemosiderosis in the spleen and erythropoietic hyperplasia were seen. At 250 mg/kg/day, hemosiderosis in the liver and kidney was also observed. Increased fat storage in the adrenal cortex was observed at 500 mg/kg/day; vacuolization of the adrenal medulla and lipidosis of the adrenal cortex were also observed in high-dose animals sacrificed moribund on day 10. Testicular effects seen at 500 mg/kg/day included degeneration, reduced sperm production, accumulation of spermatid giant cells, increased number of degenerate spermatogonia, and reduced number of sperm in epididymides. No such effects were observed at 100 or 250 mg/kg/day.

Selection of the Point of Departure for the MRL: The LOAEL of 100 mg/kg/day for hemolytic anemia was selected as the POD.

Adjustment for Intermittent Exposure: The LOAEL was adjusted from intermittent exposure to account for a continuous exposure scenario:

$LOAEL_{ADJ}$ = 100 mg/kg/day x 5 days/7 days = 71 mg/kg/day

Uncertainty Factor: $LOAEL_{ADJ}$ is divided by a total uncertainty factor of 1,000:

- 10 for use of a LOAEL
- 10 for extrapolation from animals to humans
- 10 for human variability

MRL = $LOAEL_{ADJ}$ ÷ UFs
MRL = 71 mg/kg/day ÷ (10 x 10 x 10) = 0.07 mg/kg/day

Other Additional Studies or Pertinent Information that Lend Support to this MRL: As discussed in the acute oral MRL worksheet, hemolytic anemia has been reported in several human case reports (Di Nucci et al. 1988; Fiaccadori et al. 2003; Lucantoni et al. 1991, 1992; Perbellini et al. 1985; Pozzi et al. 1985) and following inhalation and oral exposure in laboratory animals (Berdasco et al. 1988, Bruckner et al. 1989; Imberti et al. 1990; Kirk et al. 1990, 1995; Matsumoto et al. 2013; Nitschke et al. 1988; Umeda et al. 2010). Systematic review of available data indicates that hematological effects are a presumed health effect for humans (see Appendix C).

Agency Contacts (Chemical Managers): Carolyn Harper

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2-Dichloropropane
CAS Numbers: 78-87-5
Date: November 2021
Profile Status: Final
Route: Oral
Duration: Chronic

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

Rationale for Not Deriving an MRL: A chronic-duration oral MRL was not derived due to lack of adequate data for the critical effect of anemia (identified in acute- and intermediate-duration oral studies). Available chronic studies did not assess hematological parameters. Derivation of a chronic-duration oral MRL based on the lowest LOAEL identified in the available chronic studies (body weight effects) results in an MRL that is higher than the intermediate-duration oral MRL based on hematological effects and may not be protective of hematological effects. Thus, the chronic database was not considered adequate for derivation of a chronic oral MRL. Since it is unknown if hematological effects would occur at lower doses with longer exposure durations, it is considered inappropriate to base the chronic MRL on intermediate-duration data. Therefore, we cannot be sure that the intermediate MRL would be protective for chronic exposure.

Two studies evaluated the toxicity of 1,2-dichloropropane following chronic-duration oral exposure: one in rats and one in mice. The most sensitive effects identified in these studies included hepatic effects, hemosiderosis of the spleen, and body weight effects (see Table A-23). The data for these effects were not suitable for modeling. The lowest LOAEL identified was 125 mg/kg/day for body weight effects in male rats (NTP 1986); the associated NOAEL of 65 mg/kg/day would be the most sensitive POD.

After adjustment for intermittent exposure (65 mg/kg/day x 5 days/7 days), the $NOAEL_{ADJ}$ of 46 mg/kg/day divided by a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) would result in a chronic MRL of 0.5 mg/kg/day. This candidate MRL is almost 10-fold higher than the MRL derived for intermediate-duration oral exposure.

Table A-23. Summary of Candidate Critical Effects for Chronic Oral MRL for 1,2-Dichloropropane

Species	Duration/ route	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Body weight effects					
F344 rat	104 weeks 5 days/week (GO)	62	125	Decreased body weight in males	NTP 1986
Hepatic effects					
F344 rat	104 weeks 5 days/week (GO)	125	250	Clear cell foci and necrosis	NTP 1986

Table A-23. Summary of Candidate Critical Effects for Chronic Oral MRL for 1,2-Dichloropropane

Species	Duration/ route	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
B6C3F1 mouse	104 weeks 5 days/week (GO)	125	250	Hepato-cytomegaly and necrosis in males	NTP 1986
Hematological effects					
F344 rat	104 weeks 5 days/week (GO)	125	250	Slight hemosiderosis of the spleen in females (blood hematological parameters not evaluated)	NTP 1986

GO = gavage (oil vehicle); LOAEL = lowest observed adverse effect level; MRL = Minimal Risk Level; ND = not determined; NOAEL = no-observed-adverse-effect level

Agency Contacts (Chemical Managers): Carolyn Harper

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

The objective of the toxicological profile is to evaluate the potential for human exposure and the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to 1,2-dichloropropane.

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 1,2-dichloropropane. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of 1,2-dichloropropane have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of 1,2-dichloropropane are presented in Table B-1.

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

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

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

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

B.1.1 Literature Search

The current literature search was intended to update the draft toxicological profile for 1,2-dichloropropane released for public comment in 2019; thus, the literature search was restricted to studies published between December 2015 and June 2020. The following main databases were searched in June 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 1,2-dichloropropane. The query strings used for the literature search are presented in Table B-2.

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance Priority List (SPL) resource page, and other items as needed. Regulations applicable to 1,2-dichloropropane 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	
06/2020	("propylene dichloride"[nm] OR 78-87-5[rn] OR "1,2-DCP"[tw] OR "1,2-Dichloropropane"[tw] OR "1,2-Dichloropropane"[tw] OR "alpha,beta-Dichloropropane"[tw] OR "alpha,beta-Propylene dichloride"[tw] OR "D-D Mixture"[tw] OR "D-D Pilfume"[tw] OR "Dichloro-1,2 propane"[tw] OR "Dichloropropane, 1,2-"[tw] OR "Dorlone"[tw] OR "Dow-421"[tw] OR "Dowfume NC"[tw] OR "EP-201"[tw] OR "Nemex"[tw] OR "New Fieldfume"[tw] OR "Propane, 1,2-dichloro-"[tw] OR "Propylene chloride"[tw] OR "PROPYLENE DICHLORIDE"[tw] OR "Propylenedichloride"[tw] OR "R 270da"[tw] OR "Terr-o-cide"[tw] OR "Terr-o-gas"[tw] OR "Vidden D"[tw] OR "Vorlex"[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 ("Dichloropropanes"[tw] AND 1987:3000[dp]) "dichloropropane"[tw] OR "Propane dichloride"[tw] OR "Propane, dichloro-"[tw]
NTRL	
06/2020	Limits: Date Published 2015 to 2020 "1,2-DCP" OR "1,2-Dichloro-propane" OR "1,2-Dichloropropane" OR "alpha,beta-Dichloropropane" OR "alpha,beta-Propylene dichloride" OR "D-D Mixture" OR "D-D Pilfume" OR "Dichloro-1,2 propane" OR "Dichloropropane, 1,2-" OR "Dorlone" OR "Dow-421" OR "Dowfume NC" OR "EP-201" OR "Nemex" OR "New Fieldfume" OR "Propane, 1,2-dichloro-" OR "Propylene chloride" OR "PROPYLENE DICHLORIDE" OR "Propylenedichloride" OR "R 270da" OR "Terr-o-cide" OR "Terr-o-gas" OR "Vidden D" OR "Vorlex" OR "Dichloropropanes" OR "Dichloropropane" OR "Propane dichloride" OR "Propane, dichloro"
Toxcenter	
06/2020	FILE 'TOXCENTER' ENTERED AT 13:09:33 ON 29 JUN 2020 CHARGED TO COST=EH038.06.01.LB.02 L1 2285 SEA FILE=TOXCENTER 78-87-5 L2 0 SEA FILE=TOXCENTER 26198-63-0 L6 2106 SEA FILE=TOXCENTER L1 NOT PATENT/DT L8 186 SEA FILE=TOXCENTER L6 AND ED>=20151201 ACT TOXQUERY/Q --------- L10 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L11 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT,

Table B-2. Database Query Strings

Database search date	Query string
	IT)
	L12 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50)
	L13 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT
	L14 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?)
	L15 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)
	L16 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?)
	L17 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE))
	L18 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)
	L19 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)
	L20 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
	L21 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
	L22 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L23 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L24 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L25 QUE (ENDOCRIN? AND DISRUPT?)
	L26 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L27 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L28 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L29 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L30 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L31 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L32 QUE (NEPHROTOX? OR HEPATOTOX?)
	L33 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L34 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L35 QUE 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 OR L33 OR L34
	L36 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
	L37 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE) L38 QUE L35 OR L36 OR L37 L39 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) L40 QUE L38 OR L39 --------- L41 100 SEA FILE=TOXCENTER L8 AND L40 D SCAN L41 69: FILE 'TOXCENTER' ENTERED AT 09:42:29 ON 30 JUN 2020 CHARGED TO COST=EH038.06.01.LB.02 L1 157 SEA FILE=TOXCENTER 26638-19-7 NOT 78-87-5 L2 115 SEA FILE=TOXCENTER L1 NOT (PATENT/DT OR TSCATS/FS) ACT TOXQUERY/Q --------- L3 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L4 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L5 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L6 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L7 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L8 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L9 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L10 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L11 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L12 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L13 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L14 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L15 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?) L16 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?) L17 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?) L18 QUE (ENDOCRIN? AND DISRUPT?)

Table B-2. Database Query Strings

Database search date	Query string
	L19 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?) L20 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?) L21 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?) L22 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?) L23 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?) L24 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?) L25 QUE (NEPHROTOX? OR HEPATOTOX?) L26 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?) L27 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?) L28 QUE L3 OR L4 OR L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 L29 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?) L30 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE) L31 QUE L28 OR L29 OR L30 L32 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) L33 QUE L31 OR L32 --------- L34 69 SEA FILE=TOXCENTER L2 AND L33 D SCAN L34

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
06/2020	Compounds searched: 78-87-5; 26198-63-0; 26638-19-7
NTP	
06/2020	Limited 2015-present 78-87-5 26198-63-0 "1,2-DCP" "1,2-Dichloro-propane" "1,2-Dichloropropane" "alpha,beta-Dichloropropane" "alpha,beta-Propylene dichloride" "D-D Mixture" "D-D Pilfume" "Dichloro-1,2 propane" "Dichloropropane, 1,2-" "Dorlone" "Dow-421" "Dowfume NC" "EP-201" "Nemex" "New Fieldfume" "Propane, 1,2-dichloro-" "Propylene chloride" "PROPYLENE DICHLORIDE" "Propylenedichloride" "R 270da" "Terr-o-cide" "Terr-o-gas" "Vidden D" "Vorlex" "Dichloropropanes" "Dichloropropane" "26638-19-7" "Propane dichloride" "Propane, dichloro-"
NPIRS	
06/2020	PC Codes searched: 29002; 600030
Regulations.gov	
06/2020	78-87-5; 26198-63-0; 26638-19-7
NIH RePORTER	
10/2020	Search Criteria: Text Search: "1,2-DCP" OR "1,2-Dichloro-propane" OR "1,2-Dichloropropane" OR "alpha,beta-Dichloropropane" OR "alpha,beta-Propylene dichloride" OR "D-D Pilfume" OR "Dichloro-1,2 propane" OR "Dichloropropane, 1,2-" OR "Dorlone" OR "Dow-421" OR "Dowfume NC" OR "EP-201" OR "Nemex" OR "New Fieldfume" OR "Propane, 1,2-dichloro-" OR "Propylene chloride" OR "PROPYLENE DICHLORIDE" OR "Propylenedichloride" OR "R 270da" OR "Terr-o-cide" OR "Terr-o-gas" OR "Vidden D" OR "Vorlex" OR "Dichloropropanes" OR Dichloropropane (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): 340
- Number of records identified from other strategies: 28
- Total number of records to undergo literature screening: 368

B.1.2 Literature Screening

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

- 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.

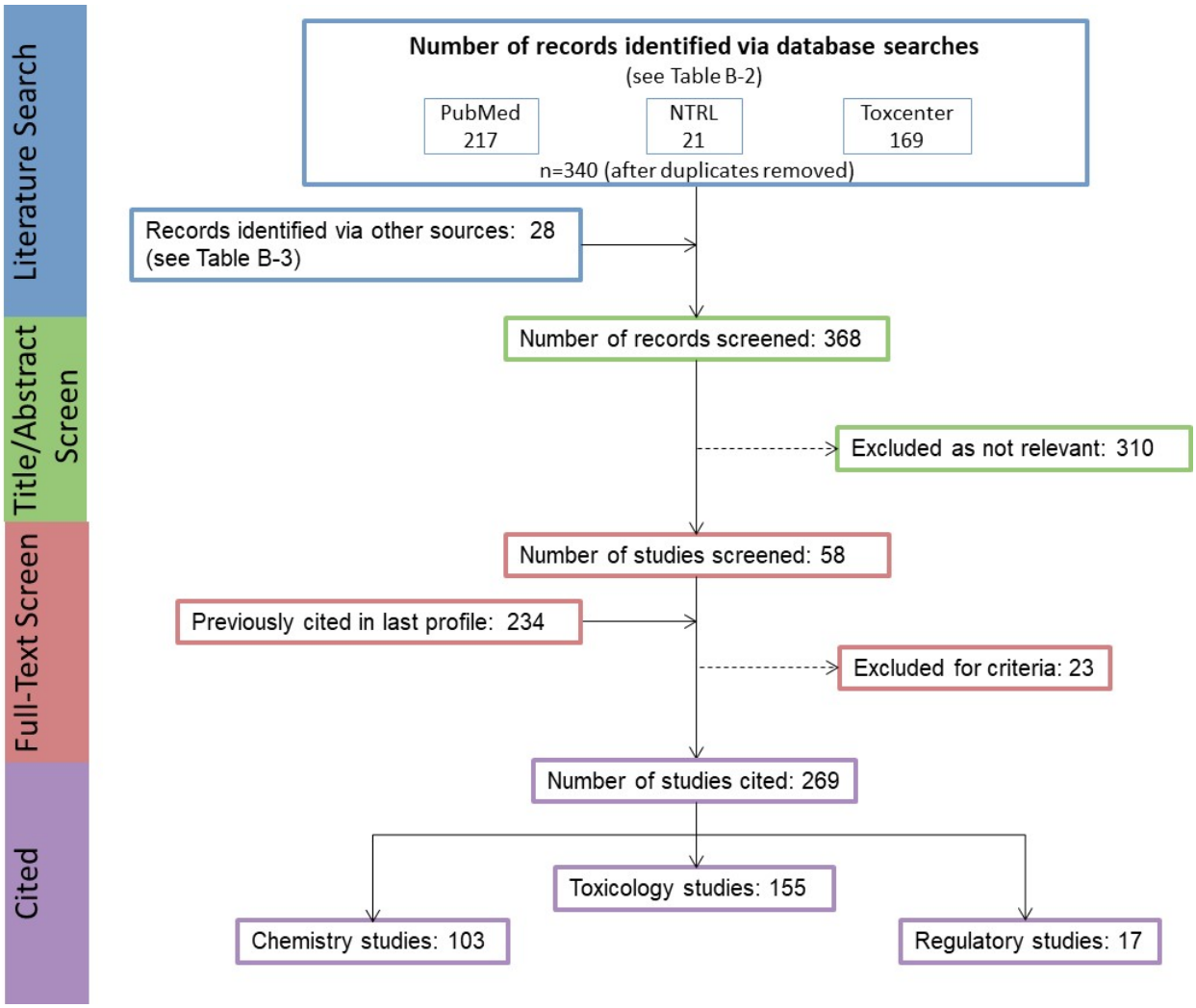
- Number of titles and abstracts screened: 368
- Number of studies considered relevant and moved to the next step: 58

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: 58
- Number of studies cited in the pre-public draft of the toxicological profile: 234
- Total number of studies cited in the profile: 269

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

Figure B-1. June 2020 Literature Search Results and Screen for 1,2-Dichloropropane



APPENDIX C. FRAMEWORK FOR ATSDR'S SYSTEMATIC REVIEW OF HEALTH EFFECTS DATA FOR 1,2-DICHLOROPROPANE

To increase the transparency of ATSDR's process of identifying, evaluating, synthesizing, and interpreting the scientific evidence on the health effects associated with exposure to 1,2-dichloropropane, ATSDR utilized a slight modification of NTP's Office of Health Assessment and Translation (OHAT) systematic review methodology (NTP 2013, 2015; Rooney et al. 2014). ATSDR's framework is an eight-step process for systematic review with the goal of identifying the potential health hazards of exposure to 1,2-dichloropropane:

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

C.1 PROBLEM FORMULATION

The objective of the toxicological profile and this systematic review was to identify the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to 1,2-dichloropropane. The inclusion criteria used to identify relevant studies examining the health effects of 1,2-dichloropropane 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 1,2-dichloropropane. 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 1,2-dichloropropane released for public comment in 2019. See Appendix B for the databases searched and the search strategy.

A total of 368 records relevant to all sections of the toxicological profile were identified (after duplicate removal).

C.2.2 Literature Screening

As described in Appendix B, a two-step process was used to screen the literature search to identify relevant studies examining the health effects of 1,2-dichloropropane.

Title and Abstract Screen. In the Title and Abstract Screen step, 368 records were reviewed; 8 documents were considered to meet the health effects inclusion criteria in Table C-1 and were moved to the next step in the process.

Full Text Screen. In the second step in the literature screening process for the systematic review, a full text review of 72 health effect documents (documents identified in the update literature search and documents cited in older versions of the profile) was performed. From those 72 documents, 121 studies were included in the qualitative review.

C.3 EXTRACT DATA FROM HEALTH EFFECTS STUDIES

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

Table C-2. Data Extracted from Individual Studies

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

A summary of the extracted data for each study is presented in the Supplemental Document for 1,2-dichloropropane and overviews of the results of the inhalation, oral, and dermal exposure studies are presented in 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 2-2, 2-3, and 2-4, respectively).

C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

Overviews of the potential health effect outcomes for 1,2-dichloropropane identified in human and animal studies are presented in Tables C-3 and C-4, respectively. The only available human studies evaluating noncancer effects are limited to case reports of accidental or intentional exposure. However, when evaluated together, these studies indicate that hematological, hepatic, renal, and neurological systems are susceptible to 1,2-dichloropropane toxicity. Animal studies examined a comprehensive set of endpoints following inhalation or oral exposure, but dermal studies were limited to acute lethality, skin irritation, and skin sensitization. Respiratory, hematological, hepatic, renal, neurological, and developmental effects were considered sensitive outcomes, i.e., effects were observed at low concentrations or doses. Studies examining these potential outcomes were carried through to Steps 4–8 of the systematic review. There were 121 studies (published in 72 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 Substance 1,2-Dichloropropane 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												5 5
Case control												1					
Population																	
Case series/reports		1 1		2 2	2 2		3 3	1 1		1 1			2 2	1 1			11 11
Oral studies																	
Cohort																	
Case control																	
Population																	
Case series/reports			3 3		3 3		5 5	2 2					2 2				
Dermal studies																	
Cohort																	
Case control																	
Population																	
Case series/reports			1 1	1 1	1 1	1 1	1 1	1 1	3 3			2 2					

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

APPENDIX C

Table C-4. Overview of the Health Outcomes for 1,2-Dichloropropane 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	9	5	5		5		27	16		1	10	3	9	3			
	3	5			3		17	8		1	5	1	8				
Intermediate-duration	10	5	12	5	12	3	14	12	3	3	7	5	6	6			1
	6	4	2	1	10		8	3			3		1	1			1
Chronic-duration	2	2	2	2	2		2	2	1		2	2	2	2			2
	2				1												2
Oral studies																	
Acute-duration	10	3		2	8		13	12			1		8	6	2		
	7			1	4		8						7	2	2		
Intermediate-duration	7	5	2	3	6	2	6	6	2	1	3	2	4	4	1		1
	4				2		5				1		1	1	1		
Chronic-duration	2	2	2	2	2	2	2	2	2		2	2	2	2			2
	1			1			2										2
Dermal studies																	
Acute-duration	2								4			1					
									4			1					
Intermediate-duration																	
Chronic-duration																	

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

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

C.5 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES

C.5.1 Risk of Bias Assessment

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The results of the risk of bias assessment for human observational studies and animal experimental studies are presented in Tables C-8 and C-9, respectively.

APPENDIX C

Table C-8. Summary of Risk of Bias Assessment for 1,2-Dichloropropane —Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings						Risk of bias tier
	Selection bias	Confounding bias	Attrition / exclusion bias	Detection bias		Selective reporting bias	
	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 exposure characterization?***	**Confidence in outcome assessment?***	All measured outcomes reported?	
Outcome: Upper respiratory effects							
Inhalation—case reports							
Rubin 1988	– –	– –	–	– –	+	–	Third
Outcome: Hematological Effects							
Inhalation – retrospective cohort							
Kumagai et al. 2013, 2014	++	–	+	– –	**+**	++	Third
Inhalation—case reports							
Lucantoni et al. 1991, 1992	– –	– –	–	– –	+	–	Third
Pozzi et al. 1985	– –	– –	–	– –	+	–	
Oral—case reports							
Di Nucci et al. 1988	– –	– –	–	– –	+	–	Third
Perbellini et al. 1985	– –	– –	–	– –	+	–	Third
Pozzi et al. 1985	– –	– –	–	– –	+	–	Third
Dermal—case reports							
Fiaccadori et al. 2003	– –	– –	–	– –	+	–	Third
Outcome: Hepatic Effects							
Inhalation—case reports							
Lucantoni et al. 1991, 1992	– –	– –	–	– –	+	–	Third
Pozzi et al. 1985	– –	– –	–	– –	+	–	Third
Kubo et al. 2015	– –	– –	–	– –	+	–	Third
Oral—case reports							Third
Chiappino and Secchi 1968	– –	– –	–	– –	+	–	Third
Di Nucci et al. 1988	– –	– –	–	– –	+	–	Third
Larcan et al. 1977	– –	– –	–	– –	+	–	Third
Perbellini et al. 1985	– –	– –	–	– –	+	–	Third

APPENDIX C

Table C-8. Summary of Risk of Bias Assessment for 1,2-Dichloropropane —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 exposure characterization?***	**Confidence in outcome assessment?***	All measured outcomes reported?	Risk of bias tier
Pozzi et al. 1985	– –	– –	–	– –	+	–	Third
Secchi and Alessio 1968	– –	– –	–	– –	+	–	Third
Thorel et al. 1986	– –	– –	–	– –	+	–	Third
Dermal—case reports							
Fiaccadori et al. 2003	– –	– –	–	– –	+	–	Third
Outcome: Renal Effects							
Inhalation—case reports							
Pozzi et al. 1985	– –	– –	–	– –	+	–	Third
Oral—case reports							
Di Nucci et al. 1988	– –	– –	–	– –	+	–	Third
Perbellini et al. 1985	– –	– –	–	– –	+	–	Third
Pozzi et al. 1985	– –	– –	–	– –	+	–	Third
Dermal—case reports							
Fiaccadori et al. 2003	– –	– –	–	– –	+	–	Third
Outcome: CNS Depression							
Inhalation—case reports							
Kwack et al. 2018	– –	– –	+	–	+	+	Third
Rubin 1988	– –	– –	–	– –	+	–	Third
Oral—case reports							
Larcan et al. 1977	– –	– –	–	– –	+	–	Third
Perbellini et al. 1985	– –	– –	–	– –	+	–	Third

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

Table C-9. Summary of Risk of Bias Assessment for 1,2-Dichloropropane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias — Was administered dose or exposure level adequately randomized?	Selection bias — Was the allocation to study groups adequately concealed?	Performance bias — Were experimental conditions identical across study groups?	Performance bias — 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?	Detection bias — **Is there confidence in the outcome assessment?***	Selective reporting bias — Were all measured outcomes reported?	Other bias — Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Outcome: Upper Respiratory Effects										
Inhalation acute exposure										
Nitschke and Johnson 1983 (rat; 2 weeks)	++	+	++	+	++	++	**++**	++	NA	First
Nitschke and Johnson 1983 (mouse; 2 weeks)	++	+	++	+	++	++	**++**	++	NA	First
Nitschke and Johnson 1983 (rabbit; 2 weeks)	++	+	++	+	++	++	**++**	++	NA	First
Inhalation intermediate exposure										
Matsumoto et al. 2013 (mouse)	++	+	++	+	++	++	**++**	++	NA	First
Nitschke et al. 1988 (rat)	++	+	++	+	++	++	**++**	++	NA	First
Nitschke et al. 1988 (mouse)	++	+	++	+	++	++	**++**	++	NA	First
Nitschke et al. 1988 (rabbit)	++	+	++	+	++	++	**++**	++	NA	First
Umeda et al. 2010 (rat)	++	+	++	+	++	++	**++**	++	NA	First
Inhalation chronic exposure										
Matsumoto et al. 2013 (mouse)	++	+	++	+	++	++	**++**	++	NA	First
Umeda et al. 2010 (rat)	++	+	++	+	++	++	**++**	++	NA	First
Outcome: Hematological Effects										
Inhalation acute exposure										
Heppel et al. 1946b (rat; 5–8 days)	–	+	++	+	+	–	**–**	+	NA	Second
Heppel et al. 1946a (guinea pig; 5 days)	–	+	++	+	+	–	**–**	+	NA	Second
Heppel et al. 1946a (rabbit; 2–8 days)	–	+	++	+	+	–	**–**	+	NA	Second
Nitschke and Johnson 1983 (rat)	++	+	++	+	++	++	**++**	++	NA	First
Nitschke and Johnson 1983 (mouse)	++	+	++	+	++	++	**++**	++	NA	First

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Table C-9. Summary of Risk of Bias Assessment for 1,2-Dichloropropane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	**Is there confidence in the outcome assessment?***	Were all measured outcomes reported?	Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Inhalation intermediate exposure										
Heppel et al. 1946b (dog)	–	–	++	–	+	–	–	+	NA	Third
Heppel et al. 1946b (rat)	–	+	++	+	+	–	–	+	NA	Second
Heppel et al. 1946a (rabbit)	–	+	++	+	+	–	–	+	NA	Second
Heppel et al. 1948 (dog)	–	+	+	+	+	–	–	+	NA	Second
Heppel et al. 1948 (rat)	–	+	+	+	+	–	–	+	NA	Second
Heppel et al. 1948 (mouse)	–	+	+	+	+	–	–	+	NA	Second
Heppel et al. 1948 (guinea pig)	–	+	+	+	+	–	–	+	NA	Second
Matsumoto et al. 2013 (mouse)	++	+	++	+	++	++	++	++	NA	First
Nitschke et al. 1988 (rat)	++	+	++	+	++	++	++	++	NA	First
Nitschke et al. 1988 (mouse)	++	+	++	+	++	++	++	++	NA	First
Nitschke et al. 1988 (rabbit)	++	+	++	+	++	++	++	++	NA	First
Umeda et al. 2010 (rat)	++	+	++	+	++	++	++	++	NA	First
Inhalation chronic exposure										
Matsumoto et al. 2013 (mouse)	++	+	++	+	++	++	++	++	NA	First
Umeda et al. 2010 (rat)	++	+	++	+	++	++	++	++	NA	First
Oral acute exposure										
Berdasco et al. 1988 (rabbit)	++	+	++	+	++	++	++	++	NA	First
Bruckner et al. 1989 (rat)	+	+	++	+	++	++	++	++	NA	First
Gi et al. 2015a (mouse; 4 days)	–	+	++	+	++	++	++	++	NA	First
Gi et al. 2015a (hamster; 4 days)	–	+	++	+	++	++	++	++	NA	First
Gorzinski and Johnson 1989 (rat)	+	+	++	+	++	++	++	++	NA	First

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Table C-9. Summary of Risk of Bias Assessment for 1,2-Dichloropropane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: 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?	Detection bias: **Is there confidence in the outcome assessment?***	Selective reporting bias: Were all measured outcomes reported?	Other bias: Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Imberti et al. 1990 (rat)	–	–	– –	–	+	++	–	+	NA	Third
Kirk et al. 1989 (rat)	++	+	++	+	++	++	++	++	NA	First
Kirk et al. 1995 (rabbit)	++	++	++	++	++	++	++	++	NA	First
Oral intermediate exposure										
Bruckner et al. 1989 (rat)	+	+	++	+	++	++	++	++	NA	First
Gi et al. 2015a (mouse)	–	+	++	+	++	++	++	++	NA	First
Gi et al. 2015a (hamster)	–	+	++	+	++	++	++	++	NA	First
Kirk et al. 1990 (rat)	++	+	++	+	++	++	++	++	NA	First
NTP 1986 (rat)	++	++	++	++	++	++	++	++	NA	First
NTP 1986 (mouse)	++	++	++	++	++	++	++	++	NA	First
Oral chronic exposure										
NTP 1986 (rat)	++	++	++	++	++	++	++	++	NA	First
NTP 1986 (mouse)	++	++	++	++	++	++	++	++	NA	First
Outcome: Hepatic Effects										
Inhalation acute exposure										
Di Nucci et al. 1990 (rat)	–	+	+	+	++	–	–	++	NA	Second
Drew et al. 1978 (rat)	–	+	+	+	++	+	–	++	NA	Second
Heppel et al. 1946a (rat; 7 hours)	– –	– –	– –	– –	+	–	– –	+	NA	Third
Heppel et al. 1946a (rat; 5–8 days)	–	+	++	+	+	–	–	+	NA	Second
Heppel et al. 1946a (mouse; 2–7 hours)	–	+	++	+	+	–	–	+	NA	Second
Heppel et al. 1946a (rabbit; 2–8 days)	–	+	++	+	+	–	–	+	NA	Second
Heppel et al. 1946a (guinea pig; 5 days)	–	+	++	+	+	–	–	+	NA	Second

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Table C-9. Summary of Risk of Bias Assessment for 1,2-Dichloropropane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	**Is there confidence in the outcome assessment?***	Were all measured outcomes reported?	Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Heppel et al. 1948 (rat)	–	+	+	+	+	–	–	+	NA	Second
Heppel et al. 1948 (mouse)	–	+	+	+	+	–	–	+	NA	Second
Heppel et al. 1948 (guinea pig)	–	+	+	+	+	–	–	+	NA	Second
Highman and Heppel 1946 (rat; 5 days)	–	+	+	+	+	–	–	+	NA	Second
Highman and Heppel 1946 (guinea pig; 7 hours)	–	+	+	+	+	–	–	+	NA	Second
Highman and Heppel 1946 (guinea pig; 2–3 days)	–	+	+	+	+	–	–	+	NA	Second
Nitschke and Johnson 1983 (rat; 6 hours)	++	+	++	+	++	++	++	++	NA	First
Nitschke and Johnson 1983 (rat; 2 weeks)	++	+	++	+	++	++	++	++	NA	First
Nitschke and Johnson 1983 (mouse; 6 hours)	++	+	++	+	++	++	++	++	NA	First
Nitschke and Johnson 1983 (mouse; 2 weeks)	++	+	++	+	++	++	++	++	NA	First
Nitschke and Johnson 1983 (rabbit; 2 weeks)	++	+	++	+	++	++	++	++	NA	First
Toyooka et al. 2017 (mouse)	–	+	++	+	++	++	+	++	NA	First
Wang et al. 2019 (mouse, up to 4 hours)	–	+	++	+	++	+	++	+	NA	First
Wang et al. 2019 (mouse, 6 hours)	–	+	++	+	++	+	++	+	NA	First
Zhang et al. 2015 (rat, 7 days)	–	+	+	+	+	++	++	++	NA	First
Zhang et al. 2015 (C57BL/6 mouse; 7 days)	–	+	+	+	+	++	++	++	NA	First
Zhang et al. 2015 (BALB mouse; 7 days)	–	+	+	+	+	++	++	++	NA	First
Zhang et al. 2015 (mouse; 14 days)	–	+	+	+	+	++	++	++	NA	First
Zhang et al. 2015 (hamster; 7 days)	–	+	+	+	+	++	++	++	NA	First

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Table C-9. Summary of Risk of Bias Assessment for 1,2-Dichloropropane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	**Is there confidence in the outcome assessment?***	Were all measured outcomes reported?	Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Zhang et al. 2015 (hamster; 14 days)	–	+	+	+	+	++	++	++	NA	First
Zhang et al. 2015 (guinea pig; 7 days)	–	+	+	+	+	++	++	++	NA	First
Inhalation intermediate exposure										
Heppel et al. 1946a (dog)	–	–	++	–	+	–	–	+	NA	Third
Heppel et al. 1946a (rat)	–	+	++	+	+	–	–	+	NA	Second
Heppel et al. 1946a (rabbit)	–	+	++	+	+	–	–	+	NA	Second
Heppel et al. 1946a (guinea pig)	–	+	++	+	+	–	–	+	NA	Second
Heppel et al. 1948 (dog)	–	+	+	+	+	–	–	+	NA	Second
Heppel et al. 1948 (rat)	–	+	+	+	+	–	–	+	NA	Second
Heppel et al. 1948 (mouse)	–	+	+	+	+	–	–	+	NA	Second
Heppel et al. 1948 (guinea pig)	–	+	+	+	+	–	–	+	NA	Second
Matsumoto et al. 2013 (mouse)	++	+	++	+	++	++	++	++	NA	First
Nitschke et al. 1988 (rat)	++	+	++	+	++	++	++	++	NA	First
Nitschke et al. 1988 (mouse)	++	+	++	+	++	++	++	++	NA	First
Nitschke et al. 1988 (rabbit)	++	+	++	+	++	++	++	++	NA	First
Umeda et al. 2010 (rat)	++	+	++	+	++	++	++	++	NA	First
Zhang et al. 2018 (mouse)	+	+	++	++	++	++	++	++	NA	First
Inhalation chronic exposure										
Matsumoto et al. 2013 (mouse)	++	+	++	+	++	++	++	++	NA	First
Umeda et al. 2010 (rat)	++	+	++	+	++	++	++	++	NA	First
Oral acute exposure										
Berdasco et al. 1988 (rabbit)	++	+	++	+	++	++	++	++	NA	First

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Table C-9. Summary of Risk of Bias Assessment for 1,2-Dichloropropane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	**Is there confidence in the outcome assessment?***	Were all measured outcomes reported?	Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Bruckner et al. 1989 (rat)	+	+	++	+	++	++	++	++	NA	First
Di Nucci et al. 1988 (rat)	–	+	+	+	++	–	–	++	NA	Second
Gi et al. 2015a (mouse; once)	–	+	++	+	++	++	++	++	NA	First
Gi et al. 2015a (mouse; 4 days)	–	+	++	+	++	++	++	++	NA	First
Gi et al. 2015a (hamster; once)	–	+	++	+	++	++	++	++	NA	First
Gi et al. 2015a (hamster; 4 days)	–	+	++	+	++	++	++	++	NA	First
Gorzinski and Johnson 1989 (rat)	+	+	++	+	++	++	++	++	NA	First
Imberti et al. 1990 (rat)	–	–	– –	–	+	++	–	+	NA	Third
Kirk et al. 1988 (rabbit)	–	–	++	–	++	++	+	++	NA	First
Kirk et al. 1989 (rat)	++	+	++	+	++	++	++	++	NA	First
Kirk et al. 1995 (rat)	++	++	++	++	++	++	++	++	NA	First
Kirk et al. 1995 (rabbit)	++	++	++	++	++	++	++	++	NA	First
Oral intermediate exposure										
Bruckner et al. 1989 (rat)	+	+	++	+	++	++	++	++	NA	First
Gi et al. 2015a (mouse)	–	+	++	+	++	++	++	++	NA	First
Gi et al. 2015a (hamster)	–	+	++	+	++	++	++	++	NA	First
Kirk et al. 1990 (rat)	++	+	++	+	++	++	++	++	NA	First
NTP 1986 (rat)	++	++	++	++	++	++	++	++	NA	First
NTP 1986 (mouse)	++	++	++	++	++	++	++	++	NA	First
Oral chronic exposure										
NTP 1986 (rat)	++	++	++	++	++	++	++	++	NA	First
NTP 1986 (mouse)	++	++	++	++	++	++	++	++	NA	First

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Table C-9. Summary of Risk of Bias Assessment for 1,2-Dichloropropane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	**Is there confidence in the outcome assessment?***	Were all measured outcomes reported?	Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Outcome: Renal Effects										
Inhalation acute exposure										
Heppel et al. 1946a (rat; 5–8 days)	–	+	++	+	+	–	–	+	NA	Second
Heppel et al. 1946a (mouse; 2–7 hours)	–	+	++	+	+	–	–	+	NA	Second
Heppel et al. 1946a (rabbit; 2–8 days)	–	+	++	+	+	–	–	+	NA	Second
Heppel et al. 1946a (guinea pig; 5 days)	–	+	++	+	+	–	–	+	NA	Second
Heppel et al. 1948 (rat)	–	+	+	+	+	–	–	+	NA	Second
Heppel et al. 1948 (mouse)	–	+	+	+	+	–	–	+	NA	Second
Heppel et al. 1948 (guinea pig)	–	+	+	+	+	–	–	+	NA	Second
Highman and Heppel 1946 (rat; 5 days)	–	+	+	+	+	–	–	+	NA	Second
Highman and Heppel 1946 (guinea pig; 7 hours)	–	+	+	+	+	–	–	+	NA	Second
Highman and Heppel 1946 (guinea pig; 2–3 days)	–	+	+	+	+	–	–	+	NA	Second
Nitschke and Johnson 1983 (rat; 6 hours)	++	+	++	+	++	++	++	++	NA	First
Nitschke and Johnson 1983 (rat; 2 weeks)	++	+	++	+	++	++	++	++	NA	First
Nitschke and Johnson 1983 (mouse; 6 hours)	++	+	++	+	++	++	++	++	NA	First
Nitschke and Johnson 1983 (mouse; 2 weeks)	++	+	++	+	++	++	++	++	NA	First
Nitschke and Johnson 1983 (rabbit; 2 weeks)	++	+	++	+	++	++	++	++	NA	First

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Table C-9. Summary of Risk of Bias Assessment for 1,2-Dichloropropane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	**Is there confidence in the outcome assessment?***	Were all measured outcomes reported?	Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Inhalation intermediate exposure										
Heppel et al. 1946a (dog)	–	–	++	–	+	–	–	+	NA	Third
Heppel et al. 1946a (rat)	–	+	++	+	+	–	–	+	NA	Second
Heppel et al. 1946a (rabbit)	–	+	++	+	+	–	–	+	NA	Second
Heppel et al. 1946a (guinea pig)	–	+	++	+	+	–	–	+	NA	Second
Heppel et al. 1948 (dog)	–	+	+	+	+	–	–	+	NA	Second
Heppel et al. 1948 (rat)	–	+	+	+	+	–	–	+	NA	Second
Heppel et al. 1948 (mouse)	–	+	+	+	+	–	–	+	NA	Second
Heppel et al. 1948 (rabbit)	–	+	+	+	+	–	–	+	NA	Second
Matsumoto et al. 2013 (mouse)	++	+	++	+	++	++	++	++	NA	First
Nitschke et al. 1988 (rat)	++	+	++	+	++	++	++	++	NA	First
Nitschke et al. 1988 (mouse)	++	+	++	+	++	++	++	++	NA	First
Nitschke et al. 1988 (rabbit)	++	+	++	+	++	++	++	++	NA	First
Umeda et al. 2010 (rat)	++	+	++	+	++	++	++	++	NA	First
Inhalation chronic exposure										
Matsumoto et al. 2013 (mouse)	++	+	++	+	++	++	++	++	NA	First
Umeda et al. 2010 (rat)	++	+	++	+	++	++	++	++	NA	First
Oral acute exposure										
Berdasco et al. 1988 (rabbit)	++	+	++	+	++	++	++	++	NA	First
Bruckner et al. 1989 (rat)	+	+	++	+	++	++	++	++	NA	First
Gi et al. 2015a (mouse; 4 days)	–	+	++	+	++	++	++	++	NA	First
Gi et al. 2015a (hamster; 4 days)	–	+	++	+	++	++	++	++	NA	First

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Table C-9. Summary of Risk of Bias Assessment for 1,2-Dichloropropane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias — Was administered dose or exposure level adequately randomized?	Selection bias — Was the allocation to study groups adequately concealed?	Performance bias — Were experimental conditions identical across study groups?	Performance bias — 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?	Detection bias — **Is there confidence in the outcome assessment?***	Selective reporting bias — Were all measured outcomes reported?	Other bias — Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Gorzinski and Johnson 1989 (rat)	+	+	++	+	++	++	++	++	NA	First
Imberti et al. 1990 (rat)	–	–	– –	–	+	++	–	+	NA	Third
Kirk et al. 1988 (rabbit)	–	–	++	–	++	++	+	++	NA	First
Kirk et al. 1989 (rat)	++	+	++	+	++	++	++	++	NA	First
Kirk et al. 1995 (rat)	++	++	++	++	++	++	++	++	NA	First
Kirk et al. 1995 (rabbit)	++	++	++	++	++	++	++	++	NA	First
NTP 1986 (rat)	+	+	++	+	++	++	++	+	NA	First
NTP 1986 (mouse)	+	+	++	+	++	++	++	+	NA	First
Oral intermediate exposure										
Bruckner et al. 1989 (rat)	+	+	++	+	++	++	++	++	NA	First
Gi et al. 2015a (mouse)	–	+	++	+	++	++	++	++	NA	First
Gi et al. 2015a (hamster)	–	+	++	+	++	++	++	++	NA	First
Kirk et al. 1990 (rat)	++	+	++	+	++	++	++	++	NA	First
NTP 1986 (rat)	++	++	++	++	++	++	++	++	NA	First
NTP 1986 (mouse)	++	++	++	++	++	++	++	++	NA	First
Oral chronic exposure										
NTP 1986 (rat)	++	++	++	++	++	++	++	++	NA	First
NTP 1986 (mouse)	++	++	++	++	++	++	++	++	NA	First
Outcome: CNS Depression										
Inhalation acute exposure										
Heppel et al. 1946a (rat; 7 hours)	– –	– –	– –	– –	+	–	–	+	NA	Third
Heppel et al. 1946a (rat; 5–8 days)	–	–	++	–	+	–	–	+	NA	Third

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Table C-9. Summary of Risk of Bias Assessment for 1,2-Dichloropropane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: 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?	Detection bias: **Is there confidence in the outcome assessment?***	Selective reporting bias: Were all measured outcomes reported?	Other bias: Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Heppel et al. 1946a (mouse; 2–7 hours)	–	–	++	–	+	–	–	+	NA	Third
Heppel et al. 1946a (guinea pig; 5 days)	–	–	++	–	+	–	–	+	NA	Third
Nitschke and Johnson 1983 (rat; 6 hours)	++	+	++	+	+	++	++	+	NA	First
Nitschke and Johnson 1983 (mouse; 6 hours)	++	+	++	+	+	++	++	+	NA	First
Sidorenko et al. 1979 (rat)	–	–	–	–	–	–	–	–	NA	Third
Sidorenko et al. 1976 (mouse)	–	–	–	–	–	–	–	–	NA	Third
Inhalation intermediate exposure										
Sidorenko et al. 1979 (rat)	–	–	–	–	–	–	–	–	NA	Third
Oral acute exposure										
Bruckner et al. 1989 (rat)	+	–	++	–	++	++	++	++	NA	First
Exxon 1981a (rat)	++	–	++	–	–	++	+	++	NA	First
Gorzinski and Johnson 1989 (rat)	+	–	++	–	++	++	++	++	NA	First
Kirk et al. 1988 (rabbit)	–	–	++	–	++	++	+	++	NA	First
Kirk et al. 1989 (rat)	++	–	++	–	++	++	++	++	NA	First
Kirk et al. 1995 (rat)	++	++	++	++	++	++	++	++	NA	First
Kirk et al. 1995 (rabbit)	++	++	++	++	++	++	++	++	NA	First
Shell Oil Co. 1982 (rat)	–	–	++	–	++	–	+	++	NA	Second
Oral intermediate exposure										
Bruckner et al. 1989 (rat)	+	–	++	–	++	++	++	++	NA	First
Johnson and Gorzinski 1988 (rat)	++	++	++	++	++	++	++	++	NA	First

APPENDIX C

Table C-9. Summary of Risk of Bias Assessment for 1,2-Dichloropropane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias — Was administered dose or exposure level adequately randomized?	Selection bias — Was the allocation to study groups adequately concealed?	Performance bias — Were experimental conditions identical across study groups?	Performance bias — 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?	Detection bias — **Is there confidence in the outcome assessment?***	Selective reporting bias — Were all measured outcomes reported?	Other bias — Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Outcome: Developmental Effects										
Oral acute exposure										
Kirk et al. 1995 (rat)	++	++	++	++	++	++	**++**	++	NA	First
Kirk et al. 1995 (rabbit)	++	++	++	++	++	++	**++**	++	NA	First
Oral intermediate exposure										
Kirk et al. 1990 (rat)	++	+	++	+	++	++	**++**	++	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 1,2-dichloropropane 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 1,2-dichloropropane and a particular outcome was given an initial confidence rating based on the key features of the individual studies examining that outcome. The presence of these key features of study design was determined for individual studies using four "yes or no" questions, which were customized for epidemiology, human controlled exposure, or experimental animal study designs. Separate questionnaires were completed for each outcome assessed in a study. The key features for observational epidemiology (cohort, population, and case-control) studies, human controlled exposure, and experimental animal studies are presented in Tables C-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 upper respiratory, hematological, hepatic, renal, neurological, and developmental effects observed in human observational studies 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.

Table C-13. Presence of Key Features of Study Design for 1,2-Dichloropropane—Observational Epidemiology Studies

Reference	Key features				Initial study confidence
	Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	
Outcome: Upper respiratory effects					
Inhalation—case reports					
Rubin 1988	No	Yes	Yes	No	Low
Outcome: Hematological Effects					
Inhalation—retrospective cohort					
Kumagai et al. 2013, 2014	No	Yes	Yes	Yes	Moderate
Inhalation—case reports					
Lucantoni et al. 1991, 1992	No	Yes	Yes	No	Low
Pozzi et al. 1985	No	Yes	Yes	No	Low
Oral—case reports					
Di Nucci et al. 1988	No	Yes	Yes	No	Low
Perbellini et al. 1985	No	Yes	Yes	No	Low
Pozzi et al. 1985	No	Yes	Yes	No	Low
Dermal—case reports					
Fiaccadori et al. 2003	No	Yes	Yes	No	Low
Outcome: Hepatic Effects					
Inhalation—case reports					
Lucantoni et al. 1991, 1992	No	Yes	Yes	No	Low
Pozzi et al. 1985	No	Yes	Yes	No	Low
Kubo et al. 2015	No	Yes	Yes	No	Low
Oral—case reports					
Chiappino and Secchi 1968	No	Yes	Yes	No	Low
Di Nucci et al. 1988	No	Yes	Yes	No	Low
Larcan et al. 1977	No	Yes	Yes	No	Low
Perbellini et al. 1985	No	Yes	Yes	No	Low
Pozzi et al. 1985	No	Yes	Yes	No	Low
Secchi and Alessio 1968	No	Yes	Yes	No	Low
Thorel et al. 1986	No	Yes	Yes	No	Low
Dermal—case reports					
Fiaccadori et al. 2003	No	Yes	Yes	No	Low
Outcome: Renal Effects					
Inhalation—case reports					
Pozzi et al. 1985	No	Yes	Yes	No	Low
Oral—case reports					
Di Nucci et al. 1988	No	Yes	Yes	No	Low
Perbellini et al. 1985	No	Yes	Yes	No	Low
Pozzi et al. 1985	No	Yes	Yes	No	Low

Table C-13. Presence of Key Features of Study Design for 1,2-Dichloropropane—Observational Epidemiology Studies

Reference	Key features: Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	Initial study confidence
Dermal—case reports					
Fiaccadori et al. 2003	No	Yes	Yes	No	Low
Outcome: CNS Depression					
Inhalation—case reports					
Kwack et al. 2018	No	Yes	Yes	No	Low
Rubin 1988	No	Yes	Yes	No	Low
Oral—case reports					
Larcan et al. 1977	No	Yes	Yes	No	Low
Perbellini et al. 1985	No	Yes	Yes	No	Low

Table C-14. Presence of Key Features of Study Design for 1,2-Dichloropropane—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: Upper Respiratory Effects					
Inhalation acute exposure					
Nitschke and Johnson 1983 (rat; 2 weeks)	Yes	Yes	Yes	No	Moderate
Nitschke and Johnson 1983 (mouse; 2 weeks)	Yes	Yes	Yes	No	Moderate
Nitschke and Johnson 1983 (rabbit; 2 weeks)	Yes	Yes	Yes	No	Moderate
Inhalation intermediate exposure					
Matsumoto et al. 2013 (mouse)	Yes	Yes	Yes	Yes	High
Nitschke et al. 1988 (rat)	Yes	Yes	Yes	Yes	High
Nitschke et al. 1988 (mouse)	Yes	Yes	Yes	Yes	High
Nitschke et al. 1988 (rabbit)	Yes	Yes	Yes	Yes	High
Umeda et al. 2010 (rat)	Yes	Yes	Yes	Yes	High
Inhalation chronic exposure					
Matsumoto et al. 2013 (mouse)	Yes	Yes	Yes	Yes	High
Umeda et al. 2010 (rat)	Yes	Yes	Yes	Yes	High
Outcome: Hematological Effects					
Inhalation acute exposure					
Heppel et al. 1946b (rat; 5–8 days)	No	Yes	No	No	Very Low

Table C-14. Presence of Key Features of Study Design for 1,2-Dichloropropane—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	
Heppel et al. 1946a (guinea pig; 5 days)	No	Yes	No	No	Very Low
Heppel et al. 1946a (rabbit; 2–8 days)	No	No	No	No	Very Low
Nitschke and Johnson 1983 (rat; 2 weeks)	Yes	Yes	Yes	Yes	High
Nitschke and Johnson 1983 (mouse; 2 weeks)	Yes	Yes	Yes	Yes	High
Inhalation intermediate exposure					
Heppel et al. 1946b (dog)	Yes	No	Yes	No	Low
Heppel et al. 1946b (rat)	Yes	Yes	No	No	Low
Heppel et al. 1946a (rabbit)	Yes	Yes	Yes	No	Moderate
Heppel et al. 1948 (dog)	Yes	Yes	No	No	Low
Heppel et al. 1948 (rat)	Yes	Yes	No	No	Low
Heppel et al. 1948 (mouse)	Yes	Yes	No	No	Low
Heppel et al. 1946a (guinea pig)	Yes	Yes	No	No	Low
Matsumoto et al. 2013 (mouse)	Yes	Yes	Yes	Yes	High
Nitschke et al. 1988 (rat)	Yes	Yes	Yes	Yes	High
Nitschke et al. 1988 (mouse)	Yes	Yes	Yes	Yes	High
Nitschke et al. 1988 (rabbit)	Yes	Yes	Yes	Yes	High
Umeda et al. 2010 (rat)	Yes	Yes	Yes	Yes	High
Inhalation chronic exposure					
Matsumoto et al. 2013 (mouse)	Yes	Yes	Yes	No	Moderate
Umeda et al. 2010 (rat)	Yes	Yes	Yes	No	Moderate
Oral acute exposure					
Berdasco et al. 1988 (rabbit)	Yes	Yes	Yes	Yes	High
Bruckner et al. 1989 (rat)	Yes	Yes	Yes	No	Moderate
Gi et al. 2015a (rat)	Yes	Yes	No	Yes	Moderate
Gi et al. 2015a (hamster)	Yes	Yes	No	Yes	Moderate
Gorzinski and Johnson 1989 (rat)	Yes	Yes	Yes	Yes	High
Imberti et al. 1990 (rat)	No	Yes	Yes	No	Low
Kirk et al. 1989 (rat)	Yes	Yes	Yes	Yes	High
Kirk et al. 1995 (rabbit)	Yes	Yes	Yes	Yes	High
Oral intermediate exposure					
Bruckner et al. 1989 (rat)	Yes	Yes	Yes	Yes	High
Gi et al. 2015a (mouse)	Yes	Yes	No	Yes	Moderate
Gi et al. 2015a (hamster)	Yes	Yes	Yes	Yes	High
Kirk et al. 1990 (rat)	Yes	Yes	Yes	Yes	High
NTP 1986 (rat)	Yes	Yes	No	Yes	Moderate
NTP 1986 (mouse)	Yes	Yes	No	Yes	Moderate

Table C-14. Presence of Key Features of Study Design for 1,2-Dichloropropane—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					
NTP 1986 (rat)	Yes	Yes	No	Yes	Moderate
NTP 1986 (mouse)	Yes	Yes	No	Yes	Moderate
Outcome: Hepatic Effects					
Inhalation acute exposure					
Di Nucci et al. 1990 (rat)	Yes	Yes	No	No	Low
Drew et al. 1978 (rat)	Yes	Yes	No	No	Low
Heppel et al. 1946a (rat; 7 hours)	No	No	Yes	No	Very Low
Heppel et al. 1946a (rat; 5–8 days)	No	Yes	Yes	No	Low
Heppel et al. 1946a (mouse; 2–7 hours)	No	Yes	Yes	No	Low
Heppel et al. 1946a (rabbit; 2–8 days)	No	No	Yes	No	Very Low
Heppel et al. 1946a (guinea pig; 5 days)	No	Yes	Yes	No	Low
Heppel et al. 1948 (rat)	Yes	Yes	Yes	No	Moderate
Heppel et al. 1948 (mouse)	Yes	Yes	Yes	No	Moderate
Heppel et al. 1948 (guinea pig)	Yes	Yes	Yes	No	Moderate
Highman and Heppel 1946 (rat; 5 days)	Yes	Yes	Yes	No	Moderate
Highman and Heppel 1946 (guinea pig; 7 hours)	Yes	Yes	Yes	No	Moderate
Highman and Heppel 1946 (guinea pig; 2–3 days)	Yes	Yes	Yes	No	Moderate
Nitschke and Johnson 1983 (rat; 6 hours)	Yes	Yes	Yes	No	Moderate
Nitschke and Johnson 1983 (rat; 2 weeks)	Yes	Yes	Yes	No	Moderate
Nitschke and Johnson 1983 (mouse; 6 hours)	Yes	Yes	Yes	No	Moderate
Nitschke and Johnson 1983 (mouse; 2 weeks)	Yes	Yes	Yes	No	Moderate
Nitschke and Johnson 1983 (rabbit; 2 weeks)	Yes	Yes	Yes	No	Moderate
Toyooka et al. 2017	Yes	NR	No	No	Very Low
Wang et al. 2019 (mouse, up to 4 hours)	Yes	Yes	Yes	Yes	High
Wang et al. 2019 (mouse, 6 hours)	Yes	Yes	Yes	Yes	High
Zhang et al. 2015 (rat; 7 days)	Yes	No	Yes	No	Low
Zhang et al. 2015 (C57BL/6 mouse; 7 days)	Yes	No	Yes	No	Low
Zhang et al. 2015 (BALB mouse; 7 days)	Yes	No	Yes	No	Low
Zhang et al. 2015 (mouse; 14 days)	Yes	Yes	Yes	No	Moderate
Zhang et al. 2015 (hamster; 7 days)	Yes	No	Yes	No	Low
Zhang et al. 2015 (hamster; 14 days)	Yes	Yes	Yes	No	Moderate
Zhang et al. 2015 (guinea pig; 7 days)	Yes	No	Yes	No	Low

Table C-14. Presence of Key Features of Study Design for 1,2-Dichloropropane—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
Inhalation intermediate exposure					
Heppel et al. 1946a (dog)	Yes	Yes	Yes	No	Moderate
Heppel et al. 1946a (rat)	Yes	Yes	Yes	No	Moderate
Heppel et al. 1946a (rabbit)	Yes	Yes	Yes	No	Moderate
Heppel et al. 1946a (guinea pig)	Yes	Yes	Yes	No	Moderate
Heppel et al. 1948 (dog)	Yes	Yes	Yes	No	Moderate
Heppel et al. 1948 (rat)	Yes	Yes	Yes	No	Moderate
Heppel et al. 1948 (mouse)	Yes	Yes	Yes	No	Moderate
Matsumoto et al. 2013 (mouse)	Yes	Yes	Yes	Yes	High
Nitschke et al. 1988 (rat)	Yes	Yes	Yes	Yes	High
Nitschke et al. 1988 (mouse)	Yes	Yes	Yes	Yes	High
Nitschke et al. 1988 (rabbit)	Yes	Yes	Yes	Yes	High
Umeda et al. 2010 (rat)	Yes	Yes	Yes	Yes	High
Zhang et al. 2018 (mouse)	Yes	Yes	Yes	Yes	High
Inhalation chronic exposure					
Matsumoto et al. 2013 (mouse)	Yes	Yes	Yes	Yes	High
Umeda et al. 2010 (rat)	Yes	Yes	Yes	Yes	High
Oral acute exposure					
Berdasco et al. 1988 (rabbit)	Yes	Yes	No	Yes	Moderate
Bruckner et al. 1989 (rat)	Yes	Yes	Yes	Yes	High
Di Nucci et al. 1990 (rat)	Yes	Yes	No	Yes	Moderate
Gi et al. 2015a (mouse; once)	Yes	Yes	Yes	Yes	High
Gi et al. 2015a (mouse; 4 days)	Yes	Yes	Yes	Yes	High
Gi et al. 2015a (hamster; once)	Yes	Yes	Yes	Yes	High
Gi et al. 2015a (hamster; 4 days)	Yes	Yes	Yes	Yes	High
Gorzinski and Johnson 1989 (rat)	Yes	Yes	Yes	Yes	High
Imberti et al. 1990 (rat)	No	Yes	No	No	Very Low
Kirk et al. 1988 (rabbit)	Yes	No	Yes	Yes	Moderate
Kirk et al. 1989 (rat)	Yes	Yes	No	Yes	Moderate
Kirk et al. 1995 (rat)	Yes	Yes	No	Yes	Moderate
Kirk et al. 1995 (rabbit)	Yes	Yes	No	Yes	Moderate
Oral intermediate exposure					
Bruckner et al. 1989 (rat)	Yes	Yes	Yes	Yes	High
Gi et al. 2015a (mouse)	Yes	Yes	Yes	Yes	High
Gi et al. 2015a (hamster)	Yes	Yes	Yes	Yes	High
Kirk et al. 1990 (rat)	Yes	Yes	Yes	Yes	High
NTP 1986 (rat)	Yes	Yes	Yes	Yes	High

Table C-14. Presence of Key Features of Study Design for 1,2-Dichloropropane—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	
NTP 1986 (mouse)	Yes	Yes	Yes	Yes	High
Oral chronic exposure					
NTP 1986 (rat)	Yes	Yes	Yes	Yes	High
NTP 1986 (mouse)	Yes	Yes	Yes	Yes	High
Outcome: Renal Effects					
Inhalation acute exposure					
Heppel et al. 1946a (rat; 5–8 days)	No	Yes	Yes	No	Low
Heppel et al. 1946a (mouse; 2–7 hours)	No	Yes	Yes	No	Low
Heppel et al. 1946a (rabbit; 2–8 days)	No	No	Yes	No	Very Low
Heppel et al. 1946a (guinea pig; 5 days)	No	Yes	Yes	No	Low
Heppel et al. 1948 (rat)	Yes	Yes	Yes	No	Moderate
Heppel et al. 1948 (mouse)	Yes	Yes	Yes	No	Moderate
Heppel et al. 1948 (guinea pig)	Yes	Yes	Yes	No	Moderate
Highman and Heppel 1946 (rat; 5 days)	Yes	Yes	Yes	No	Moderate
Highman and Heppel 1946 (guinea pig; 7 hours)	Yes	Yes	Yes	No	Moderate
Highman and Heppel 1946 (guinea pig; 2–3 days)	Yes	Yes	Yes	No	Moderate
Nitschke and Johnson 1983 (rat; 6 hours)	Yes	Yes	Yes	No	Moderate
Nitschke and Johnson 1983 (rat; 2 weeks)	Yes	Yes	Yes	No	Moderate
Nitschke and Johnson 1983 (mouse; 6 hours)	Yes	Yes	Yes	No	Moderate
Nitschke and Johnson 1983 (mouse; 2 weeks)	Yes	Yes	Yes	No	Moderate
Nitschke and Johnson 1983 (rabbit; 2 weeks)	Yes	Yes	Yes	No	Moderate
Inhalation intermediate exposure					
Heppel et al. 1946a (dog)	Yes	Yes	Yes	No	Moderate
Heppel et al. 1946a (rat)	Yes	Yes	Yes	No	Moderate
Heppel et al. 1946a (rabbit)	Yes	Yes	Yes	No	Moderate
Heppel et al. 1946a (guinea pig)	Yes	Yes	Yes	No	Moderate
Heppel et al. 1948 (dog)	Yes	Yes	Yes	No	Moderate
Heppel et al. 1948 (rat)	Yes	Yes	Yes	No	Moderate
Heppel et al. 1948 (mouse)	Yes	Yes	Yes	No	Moderate
Heppel et al. 1948 (guinea pig)	Yes	Yes	Yes	No	Moderate
Matsumoto et al. 2013 (mouse)	Yes	Yes	Yes	Yes	High
Nitschke et al. 1988 (rat)	Yes	Yes	Yes	Yes	High
Nitschke et al. 1988 (mouse)	Yes	Yes	Yes	Yes	High

Table C-14. Presence of Key Features of Study Design for 1,2-Dichloropropane—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
Nitschke et al. 1988 (rabbit)	Yes	Yes	Yes	Yes	High
Umeda et al. 2010 (rat)	Yes	Yes	Yes	Yes	High
Inhalation chronic exposure					
Matsumoto et al. 2013 (mouse)	Yes	Yes	Yes	Yes	High
Umeda et al. 2010 (rat)	Yes	Yes	Yes	Yes	High
Oral acute exposure					
Berdasco et al. 1988 (rabbit)	Yes	Yes	No	Yes	Moderate
Bruckner et al. 1989 (rat)	Yes	Yes	Yes	No	Moderate
Gi et al. 2015a (mouse; 4 days)	Yes	Yes	Yes	Yes	High
Gi et al. 2015a (hamster; 4 days)	Yes	Yes	Yes	Yes	High
Gorzinski and Johnson 1989 (rat)	Yes	Yes	Yes	Yes	High
Imberti et al. 1990 (rat)	No	Yes	No	No	Very Low
Kirk et al. 1988 (rabbit)	Yes	No	Yes	Yes	Moderate
Kirk et al. 1989 (rat)	Yes	Yes	No	Yes	Moderate
Kirk et al. 1995 (rat)	Yes	Yes	No	Yes	Moderate
Kirk et al. 1995 (rabbit)	Yes	Yes	No	Yes	Moderate
NTP 1986 (rat)	Yes	Yes	No	Yes	Moderate
NTP 1986 (mouse)	Yes	Yes	No	Yes	Moderate
Oral intermediate exposure					
Bruckner et al. 1989 (rat)	Yes	Yes	Yes	No	Moderate
Gi et al. 2015a (mouse)	Yes	Yes	Yes	Yes	High
Gi et al. 2015a (hamster)	Yes	Yes	Yes	Yes	High
Kirk et al. 1990 (rat)	Yes	Yes	Yes	Yes	High
NTP 1986 (rat)	Yes	Yes	Yes	Yes	High
NTP 1986 (mouse)	Yes	Yes	Yes	Yes	High
Oral chronic exposure					
NTP 1986 (rat)	Yes	Yes	Yes	Yes	High
NTP 1986 (mouse)	Yes	Yes	Yes	Yes	High
Outcome: CNS Depression					
Inhalation acute exposure					
Heppel et al. 1946a (rat; 7 hours)	No	Yes	Yes	No	Low
Heppel et al. 1946a (rat; 5–8 days)	No	Yes	Yes	No	Low
Heppel et al. 1946a (mouse; 2–7 hours)	No	Yes	Yes	No	Low
Heppel et al. 1946a (guinea pig; 5 days)	No	Yes	Yes	No	Low
Nitschke and Johnson 1983 (rat; 6 hours)	Yes	Yes	Yes	No	Moderate
Nitschke and Johnson 1983 (mouse; 6 hours)	Yes	Yes	Yes	No	Moderate

Table C-14. Presence of Key Features of Study Design for 1,2-Dichloropropane—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	
Sidorenko et al. 1979 (rat)	Yes	NR	NR	No	Very low
Sidorenko et al. 1976 (mouse)	No	NR	Yes	No	Very low
Inhalation intermediate exposure					
Sidorenko et al. 1979 (rat)	Yes	NR	NR	No	Very low
Oral acute exposure					
Bruckner et al. 1989 (rat)	Yes	Yes	Yes	No	Moderate
Exxon 1981a (rat)	No	Yes	Yes	No	Low
Gorzinski and Johnson 1989 (rat)	Yes	Yes	Yes	Yes	High
Kirk et al. 1988 (rabbit)	Yes	No	Yes	Yes	Moderate
Kirk et al. 1989 (rat)	Yes	Yes	Yes	Yes	High
Kirk et al. 1995 (rat)	Yes	Yes	Yes	No	Moderate
Kirk et al. 1995 (rabbit)	Yes	Yes	Yes	No	Moderate
Shell Oil Co. 1982 (rat)	No	Yes	Yes	Yes	Moderate
Oral intermediate exposure					
Bruckner et al. 1989 (rat)	Yes	Yes	Yes	No	Moderate
Johnson and Gorzinski 1988 (rat)	Yes	Yes	Yes	Yes	High
Outcome: Developmental Effects					
Oral acute exposure					
Kirk et al. 1995 (rat)	Yes	Yes	Yes	Yes	High
Kirk et al. 1995 (rabbit)	Yes	Yes	Yes	Yes	High
Oral intermediate exposure					
Kirk et al. 1990 (rat)	Yes	Yes	No	Yes	Moderate

NR = not reported

Table C-15. Initial Confidence Rating for 1,2-Dichloropropane Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Upper Respiratory Effects		
Inhalation acute exposure		
Human studies		
Rubin 1988	Low	Low
Inhalation acute exposure		
Nitschke and Johnson 1983 (rat; 2 weeks)	Moderate	Moderate
Nitschke and Johnson 1983 (mouse; 2 weeks)	Moderate	
Nitschke and Johnson 1983 (rabbit; 2 weeks)	Moderate	
Inhalation intermediate exposure		
Animal studies		
Matsumoto et al. 2013 (mouse)	High	High
Nitschke et al. 1988 (rat)	High	
Nitschke et al. 1988 (mouse)	High	
Nitschke et al. 1988 (rabbit)	High	
Umeda et al. 2010 (rat)	High	
Inhalation chronic exposure		
Animal studies		
Matsumoto et al. 2013 (mouse)	High	High
Umeda et al. 2010 (rat)	High	
Outcome: Hematological Effects		
Inhalation acute exposure		
Human Studies		
Lucantoni et al. 1991, 1992	Low	Low
Pozzi et al. 1985	Low	
Animal studies		
Heppel et al. 1946b (rat; 5–8 days)	Very Low	High
Heppel et al. 1946a (guinea pig; 5 days)	Very Low	
Heppel et al. 1946a (rabbit; 2–8 days)	Very Low	
Nitschke and Johnson 1983 (rat; 2 weeks)	High	
Nitschke and Johnson 1983 (mouse; 2 weeks)	High	
Inhalation intermediate exposure		
Animal studies		
Heppel et al. 1946b (dog)	Low	High
Heppel et al. 1946b (rat)	Low	
Heppel et al. 1946a (rabbit)	Moderate	
Heppel et al. 1948 (dog)	Low	
Heppel et al. 1948 (rat)	Low	
Heppel et al. 1948 (mouse)	Low	
Heppel et al. 1946a (guinea pig)	Low	
Matsumoto et al. 2013 (mouse)	High	

Table C-15. Initial Confidence Rating for 1,2-Dichloropropane Health Effects Studies

	Initial study confidence	Initial confidence rating
Nitschke et al. 1988 (rat)	High	
Nitschke et al. 1988 (mouse)	High	
Nitschke et al. 1988 (rabbit)	High	
Umeda et al. 2010 (rat)	High	
Inhalation chronic exposure		
Human studies		
Kumagai et al. 2013, 2014	Moderate	Moderate
Animal studies		
Matsumoto et al. 2013 (mouse)	High	High
Umeda et al. 2010 (rat)	High	
Oral acute exposure		
Human studies		
Di Nucci et al. 1988	Low	
Perbellini et al. 1985	Low	Low
Pozzi et al. 1985	Low	
Animal studies		
Berdasco et al. 1988 (rabbit)	High	
Bruckner et al. 1989 (rat)	Moderate	
Gi et al. 2015a (rat)	Moderate	
Gi et al. 2015a (hamster)	Moderate	High
Gorzinski and Johnson 1989 (rat)	High	
Imberti et al. 1990 (rat)	Low	
Kirk et al. 1989 (rat)	High	
Kirk et al. 1995 (rabbit)	High	
Oral intermediate exposure		
Animal studies		
Bruckner et al. 1989 (rat)	High	
Gi et al. 2015a (mouse)	Moderate	
Gi et al. 2015a (hamster)	High	High
Kirk et al. 1990 (rat)	High	
NTP 1986 (rat)	Moderate	
NTP 1986 (mouse)	Moderate	
Oral chronic exposure		
Animal studies		
NTP 1986 (rat)	Moderate	Moderate
NTP 1986 (mouse)	Moderate	

Table C-15. Initial Confidence Rating for 1,2-Dichloropropane Health Effects Studies

	Initial study confidence	Initial confidence rating
Dermal acute exposure		
Human studies		
Fiaccadori et al. 2003	Low	Low
Outcome: Hepatic Effects		
Inhalation acute exposure		
Human studies		
Lucantoni et al. 1991, 1992	Low	Low
Pozzi et al. 1985	Low	
Animal studies		
Di Nucci et al. 1990 (rat)	Low	Moderate
Drew et al. 1978 (rat)	Low	
Heppel et al. 1946a (rat; 7 hours)	Very Low	
Heppel et al. 1946a (rat; 5–8 days)	Low	
Heppel et al. 1946a (mouse; 2–7 hours)	Low	
Heppel et al. 1946a (rabbit; 2–8 days)	Very Low	
Heppel et al. 1946a (guinea pig; 5 days)	Low	
Heppel et al. 1948 (rat)	Moderate	
Heppel et al. 1948 (mouse)	Moderate	
Heppel et al. 1948 (guinea pig)	Moderate	
Highman and Heppel 1946 (rat; 5 days)	Moderate	
Highman and Heppel 1946 (guinea pig; 7 hours)	Moderate	
Highman and Heppel 1946 (guinea pig; 2–3 days)	Moderate	
Nitschke and Johnson 1983 (rat; 6 hours)	Moderate	
Nitschke and Johnson 1983 (rat; 2 weeks)	Moderate	
Nitschke and Johnson 1983 (mouse; 6 hours)	Moderate	
Nitschke and Johnson 1983 (mouse; 2 weeks)	Moderate	
Nitschke and Johnson 1983 (rabbit; 2 weeks)	Moderate	
Toyooka et al. 2017	Very Low	
Wang et al. 2019 (mouse, up to 4 hours)	High	
Wang et al. 2019 (mouse, 6 hours)	High	
Zhang et al. 2015 (rat; 7 days)	Low	
Zhang et al. 2015 (C57BL/6 mouse; 7 days)	Low	
Zhang et al. 2015 (BALB mouse; 7 days)	Low	
Zhang et al. 2015 (mouse; 14 days)	Moderate	
Zhang et al. 2015 (hamster; 7 days)	Low	
Zhang et al. 2015 (hamster; 14 days)	Moderate	
Zhang et al. 2015 (guinea pig;7 days)	Low	
Inhalation intermediate exposure		
Animal studies		
Heppel et al. 1946a (dog)	Moderate	High

Table C-15. Initial Confidence Rating for 1,2-Dichloropropane Health Effects Studies

	Initial study confidence	Initial confidence rating
Heppel et al. 1946a (rat)	Moderate	
Heppel et al. 1946a (rabbit)	Moderate	
Heppel et al. 1946a (guinea pig)	Moderate	
Heppel et al. 1948 (dog)	Moderate	
Heppel et al. 1948 (rat)	Moderate	
Heppel et al. 1948 (mouse)	Moderate	
Heppel et al. 1948 (rabbit)	Moderate	
Matsumoto et al. 2013 (mouse)	High	
Nitschke et al. 1988 (rat)	High	
Nitschke et al. 1988 (mouse)	High	
Nitschke et al. 1988 (rabbit)	High	
Umeda et al. 2010 (rat)	High	
Zhang et al. 2018 (mouse)	High	
Inhalation chronic exposure		
Human studies		
Kubo et al. 2015	Low	Low
Animal studies		
Matsumoto et al. 2013 (mouse)	High	High
Umeda et al. 2010 (rat)	High	
Oral acute exposure		
Human studies		
Chiappino and Secchi 1968	Low	
Di Nucci et al. 1988	Low	
Larcan et al. 1977	Low	
Perbellini et al. 1985	Low	Low
Pozzi et al. 1985	Low	
Secchi and Alessio 1968	Low	
Thorel et al. 1986	Low	
Animal studies		
Berdasco et al. 1988 (rabbit)	Moderate	
Bruckner et al. 1989 (rat)	High	
Di Nucci et al. 1988 (rat)	Moderate	
Gi et al. 2015a (mouse; once)	High	
Gi et al. 2015a (mouse; 4 days)	High	
Gi et al. 2015a (hamster; once)	High	High
Gi et al. 2015a (hamster; 4 days)	High	
Gorzinski and Johnson 1989 (rat)	High	
Imberti et al. 1990 (rat)	Very Low	
Kirk et al. 1988 (rabbit)	Moderate	
Kirk et al. 1989 (rat)	Moderate	

Table C-15. Initial Confidence Rating for 1,2-Dichloropropane Health Effects Studies

	Initial study confidence	Initial confidence rating
Kirk et al. 1995 (rat)	Moderate	
Kirk et al. 1995 (rabbit)	Moderate	
Oral intermediate exposure		
Animal studies		
Bruckner et al. 1989 (rat)	High	
Gi et al. 2015a (mouse)	High	
Gi et al. 2015a (hamster)	High	High
Kirk et al. 1990 (rat)	High	
NTP 1986 (rat)	High	
NTP 1986 (mouse)	High	
Oral chronic exposure		
Animal studies		
NTP 1986 (rat)	High	High
NTP 1986 (mouse)	High	
Dermal acute exposure		
Human studies		
Fiaccadori et al. 2003	Low	Low
Outcome: Renal Effects		
Inhalation acute exposure		
Human studies		
Pozzi et al. 1985	Low	Low
Animal studies		
Heppel et al. 1946a (rat; 5–8 days)	Low	
Heppel et al. 1946a (mouse; 2–7 hours)	Low	
Heppel et al. 1946a (rabbit; 2–8 days)	Very Low	
Heppel et al. 1946a (guinea pig; 5 days)	Low	
Heppel et al. 1948 (rat)	Moderate	
Heppel et al. 1948 (mouse)	Moderate	
Heppel et al. 1948 (guinea pig)	Moderate	
Highman and Heppel 1946 (rat; 5 days)	Moderate	Moderate
Highman and Heppel 1946 (guinea pig; 7 hours)	Moderate	
Highman and Heppel 1946 (guinea pig; 2–3 days)	Moderate	
Nitschke and Johnson 1983 (rat; 6 hours)	Moderate	
Nitschke and Johnson 1983 (rat; 2 weeks)	Moderate	
Nitschke and Johnson 1983 (mouse; 6 hours)	Moderate	
Nitschke and Johnson 1983 (mouse; 2 weeks)	Moderate	
Nitschke and Johnson 1983 (rabbit; 2 weeks)	Moderate	
Inhalation intermediate exposure		
Animal studies		
Heppel et al. 1946a (dog)	Moderate	High

Table C-15. Initial Confidence Rating for 1,2-Dichloropropane Health Effects Studies

	Initial study confidence	Initial confidence rating
Heppel et al. 1946a (rat)	Moderate	
Heppel et al. 1946a (rabbit)	Moderate	
Heppel et al. 1946a (guinea pig)	Moderate	
Heppel et al. 1948 (dog)	Moderate	
Heppel et al. 1948 (rat)	Moderate	
Heppel et al. 1948 (mouse)	Moderate	
Heppel et al. 1948 (guinea pig)	Moderate	
Matsumoto et al. 2013 (mouse)	High	
Nitschke et al. 1988 (rat)	High	
Nitschke et al. 1988 (mouse)	High	
Nitschke et al. 1988 (rabbit)	High	
Umeda et al. 2010 (rat)	High	
Inhalation chronic exposure		
Animal studies		
Matsumoto et al. 2013 (mouse)	High	High
Umeda et al. 2010 (rat)	High	
Oral acute exposure		
Human studies		
Di Nucci et al. 1988	Low	
Perbellini et al. 1985	Low	Low
Pozzi et al. 1985	Low	
Animal studies		
Berdasco et al. 1988 (rabbit)	Moderate	
Bruckner et al. 1989 (rat)	Moderate	
Gi et al. 2015a (mouse; 4 days)	High	
Gi et al. 2015a (hamster; 4 days)	High	
Gorzinski and Johnson 1989 (rat)	High	
Imberti et al. 1990 (rat)	Very Low	
Kirk et al. 1988 (rabbit)	Moderate	High
Kirk et al. 1989 (rat)	Moderate	
Kirk et al. 1995 (rat)	Moderate	
Kirk et al. 1995 (rabbit)	Moderate	
NTP 1986 (rat)	Moderate	
NTP 1986 (mouse)	Moderate	
Oral intermediate exposure		
Animal studies		
Bruckner et al. 1989 (rat)	Moderate	
Gi et al. 2015a (mouse)	High	High
Gi et al. 2015a (hamster)	High	
Kirk et al. 1990 (rat)	High	

Table C-15. Initial Confidence Rating for 1,2-Dichloropropane Health Effects Studies

	Initial study confidence	Initial confidence rating
NTP 1986 (rat)	High	
NTP 1986 (mouse)	High	
Oral chronic exposure		
Animal studies		
NTP 1986 (rat)	High	High
NTP 1986 (mouse)	High	
Dermal acute exposure		
Human studies		
Fiaccadori et al. 2003	Low	Low
Outcome: CNS Depression		
Inhalation acute exposure		
Human studies		
Kwack et al. 2018	Low	Low
Rubin 1988	Low	
Animal studies		
Heppel et al. 1946a (rat; 7 hours)	Low	Moderate
Heppel et al. 1946a (rat; 5–8 days)	Low	
Heppel et al. 1946a (mouse; 2–7 hours)	Low	
Heppel et al. 1946a (guinea pig; 5 days)	Low	
Nitschke and Johnson 1983 (rat; 6 hours)	Moderate	
Nitschke and Johnson 1983 (mouse; 6 hours)	Moderate	
Sidorenko et al. 1976 (mouse)	Very low	
Sidorenko et al. 1979 (rat)	Very low	
Inhalation intermediate exposure		
Animal studies		
Sidorenko et al. 1979 (rat)	Very low	Very Low
Oral acute exposure		
Human studies		
Larcan et al. 1977	Low	Low
Perbellini et al. 1985	Low	
Animal studies		
Bruckner et al. 1989 (rat)	Moderate	High
Exxon 1981a (rat)	Low	
Gorzinski and Johnson 1989 (rat)	High	
Kirk et al. 1988 (rabbit)	Moderate	
Kirk et al. 1989 (rat)	High	
Kirk et al. 1995 (rat)	Moderate	
Kirk et al. 1995 (rabbit)	Moderate	
Shell Oil Co. 1982 (rat)	Moderate	

Table C-15. Initial Confidence Rating for 1,2-Dichloropropane Health Effects Studies

	Initial study confidence	Initial confidence rating
Oral intermediate exposure		
Animal studies		
Bruckner et al. 1989 (rat)	Moderate	High
Johnson and Gorzinski 1988 (rat)	High	
Outcome: Developmental Effects		
Oral acute exposure		
Animal studies		
Kirk et al. 1995 (rat)	High	High
Kirk et al. 1995 (rabbit)	High	
Oral intermediate exposure		
Animal studies		
Kirk et al. 1990 (rat)	Moderate	Moderate

C.6.2 Adjustment of the Confidence Rating

The initial confidence rating was then downgraded or upgraded depending on whether there were substantial issues that would decrease or increase confidence in the body of evidence. The nine properties of the body of evidence that were considered are listed below. The summaries of the assessment of the confidence in the body of evidence for upper respiratory, hematological, hepatic, renal, CNS depression, and developmental 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 1,2-dichloropropane exposure is presented in Table C-17.

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

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

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Outcome: Upper Respiratory Effects			
Human studies	Low	-2 risk of bias	Very Low
Animal studies	High	+1 consistency in findings; +1 large magnitude of effect	High
Outcome: Hematological Effects			
Human studies	Low	-2 risk of bias, +1 consistency in findings	Very Low
Animal studies	High	None	High
Outcome: Hepatic Effects			
Human studies	Low	-2 risk of bias, +1 consistency in findings	Very Low
Animal studies	High	+1 consistency in findings	High
Outcome: Renal Effects			
Human studies	Low	-2 risk of bias	Very Low
Animal studies	High	-2 inconsistency	Low
Outcome: CNS Depression			
Human studies	Low	-2 risk of bias	Very Low
Animal studies	High	+1 consistency in findings	High
Outcome: Developmental Effects			
Animals studies	High	None	High

Table C-17. Confidence in the Body of Evidence for 1,2-Dichloropropane

	Confidence in body of evidence	
Outcome	Human studies	Animal studies
Upper respiratory effects	Very Low	High
Hematological effects	Very Low	High
Hepatic effects	Very Low	High
Renal effects	Very Low	Low
CNS depression	Very Low	High
Developmental effects	No data	High

- **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 1,2-dichloropropane, 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 1,2-dichloropropane is presented in Table C-18.

Table C-18. Level of Evidence of Health Effects for 1,2-Dichloropropane

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human studies			
Upper respiratory effects	Very Low	Heath effect	Inadequate
Hematological effects	Very Low	Health effect	Inadequate
Hepatic effects	Very Low	Health effect	Inadequate
Renal effects	Very Low	Health effect	Inadequate
CNS depression	Very Low	Health effect	Inadequate
Developmental effects	No data	No data	Inadequate
Animal studies			
Upper respiratory effects	High	Health effect	High
Hematological effects	High	Health effect	High
Hepatic effects	High	Health effect	High
Renal effects	Low	Mixed	Low
CNS depression	High	Health effect	High
Developmental effects	High	Health effect	High

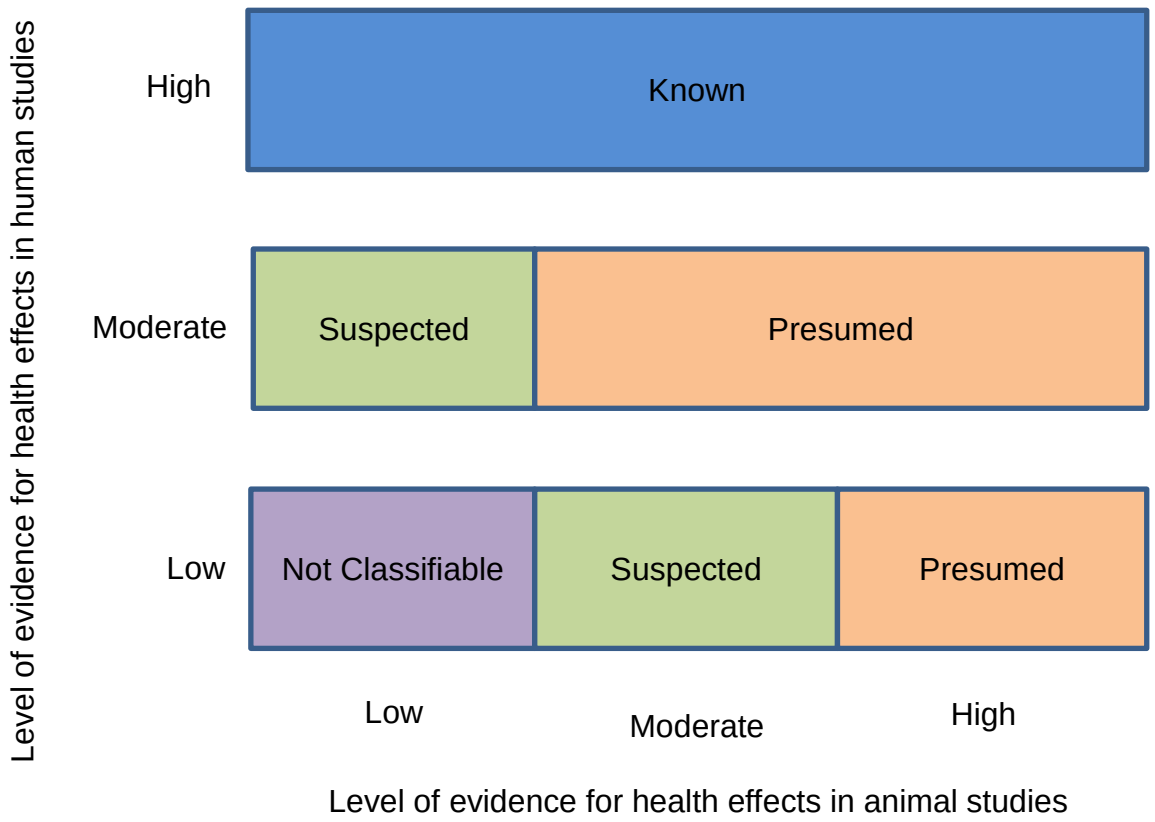
C.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

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

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

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

Figure C-1. Hazard Identification Scheme



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

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

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

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

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

The hazard identification conclusions for 1,2-dichloropropane are listed below and summarized in Table C-19.

Table C-19. Hazard Identification Conclusions for 1,2-Dichloropropane

Outcome	Hazard identification
Upper respiratory effects following inhalation exposure	Presumed health effect
Hematological effects	Presumed health effect
Hepatic effects	Presumed health effect
Renal effects	Not classifiable
CNS depression	Presumed health effect
Developmental effects	Presumed health effect

Presumed Health Effects

- Upper respiratory effects
    - Inadequate evidence from case reports of respiratory irritation following accidental industrial spills (Rubin 1988; ACGIH 2014)
    - High level of evidence of nasal lesions in rats, mice, and rabbits following intermediate or chronic inhalation exposure (Matsumoto et al. 2013; Nitschke et al. 1988; Umeda et al. 2010).
- Hematological effects
    - Although several case studies report hemolytic anemia and/or disseminating intravascular coagulation following acute inhalation, oral, or dermal exposure to 1,2-dichloropropane at unknown exposure levels (Di Nucci et al. 1988; Fiaccadori et al. 2003; Lucantoni et al. 1991, 1992; Perbellini et al. 1985; Pozzi et al. 1985), the human data were considered inadequate for evaluating the potential hazard due to the low initial confidence in these studies and the high risk of bias.
    - High level of evidence for hemolytic anemia in laboratory animals following inhalation or oral exposure (Berdasco et al. 1988; Bruckner et al. 1989; Imberti et al. 1990; Kirk et al. 1990, 1995; Matsumoto et al. 2013; Nitschke et al. 1988; Umeda et al. 2010).
- Hepatic effects
    - Although a number of case reports indicate that the liver is a target of toxicity following inhalation, oral, or dermal exposure to 1,2-dichloropropane at unknown exposure levels (Chiappino and Secchi 1968; Di Nucci et al. 1988; Fiaccadori et al. 2003; Larcan et al. 1977; Lucantoni et al. 1991, 1992; Kubo et al. 2015; Perbellini et al. 1985; Pozzi et al. 1985; Secchi and Alessio 1968; Thorel et al. 1986), the human data were considered inadequate for evaluating the potential hazard due to the low initial confidence in these studies and the high risk of bias.
    - High level of evidence of hepatic toxicity in laboratory animals following inhalation or oral exposure (Bruckner et al. 1989; Heppel et al. 1946a, 1948; Highman and Heppel

1946; Gorzinski and Johnson 1989; Gi et al. 2015a; Kirk et al. 1990; Matsumoto et al. 2013; NTP 1986; Umeda et al. 2010; Zhang et al. 2015).

- CNS depression
  - Although several case studies report severe CNS depression following acute inhalation or oral exposure to 1,2-dichloropropane at unknown exposure levels (Larcan et al. 1977; Perbellini et al. 1985; see also reviews by ACGIH 2014; EPA 2016a; IARC 2017), the human data were considered inadequate for evaluating the potential hazard due to the low initial confidence in these studies and the high risk of bias.
  - High level of evidence from acute oral studies in laboratory animals (Bruckner et al. 1989; Exxon 1981a; Gorzinski and Johnson 1989; Kirk et al. 1989; Shell Oil Co. 1982) and low level of evidence from acute inhalation studies (Heppel et al. 1946a).
- Developmental effects
  - No data are available on whether inhalation, oral, or dermal exposure to 1,2-dichloropropane alters human development.
  - High level evidence in oral animal studies based on delayed ossification following gestational exposure in rats and rabbits and decreased neonatal survival and body weight in a 2-generation study in rats at doses associated with maternal toxicity (Kirk et al. 1990, 1995). No data are available on whether inhalation exposure to 1,2-dichloropropane alters animal development.

Not Classifiable Effects

- Renal effects
  - A few case reports indicate that the kidney is a target of toxicity following inhalation or oral exposure to 1,2-dichloropropane at unknown exposure levels (Di Nucci et al. 1988; Perbellini et al. 1985; Pozzi et al. 1985); however, the human data were considered inadequate for evaluating the potential hazard due to the low initial confidence in these studies and the high risk of bias.
  - Low evidence of renal toxicity in laboratory animals due to inconsistent evidence in inhalation studies (Heppel et al. 1946a, 1948; Highman and Heppel 1946; Matsumoto et al. 2013) and lack of evidence in oral studies (Bruckner et al. 1989; Gi et al. 2015a; Gorzinski and Johnson 1989; Kirk et al. 1990; NTP 1986).

APPENDIX D. USER'S GUIDE

Chapter 1. Relevance to Public Health

This chapter provides an overview of U.S. exposures, a summary of health effects based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information, and an overview of the minimal risk levels. This is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

Minimal Risk Levels (MRLs)

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

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Section 1.2, Summary of Health Effects, contains basic information known about the substance. Other sections, such as Section 3.2 Children and Other Populations that are Unusually Susceptible and Section 3.4 Interactions with Other Substances, provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a

substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables that are provided in Chapter 2. Detailed discussions of the MRLs are presented in Appendix A.

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species and MRLs to humans for noncancer endpoints. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE tables and figures follow. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

TABLE LEGEND

See Sample LSE Table (page D-5)

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

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

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

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

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

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

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), food intake (FI), gross necropsy (GN), hematology (HE), histopathology (HP), immune function (IX), lethality (LE),neurological function (NX), organ function (OF), ophthalmology (OP), organ weight (OW), reproductive function (RX), urinalysis (UR), and water intake (WI).

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

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

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

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

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

FIGURE LEGEND

See Sample LSE Figure (page D-6)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(12) Exposure period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the chronic exposure period are illustrated.

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

(14) Levels of exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(15) LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).

(16) CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.

(17) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

APPENDIX D

Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral (1)

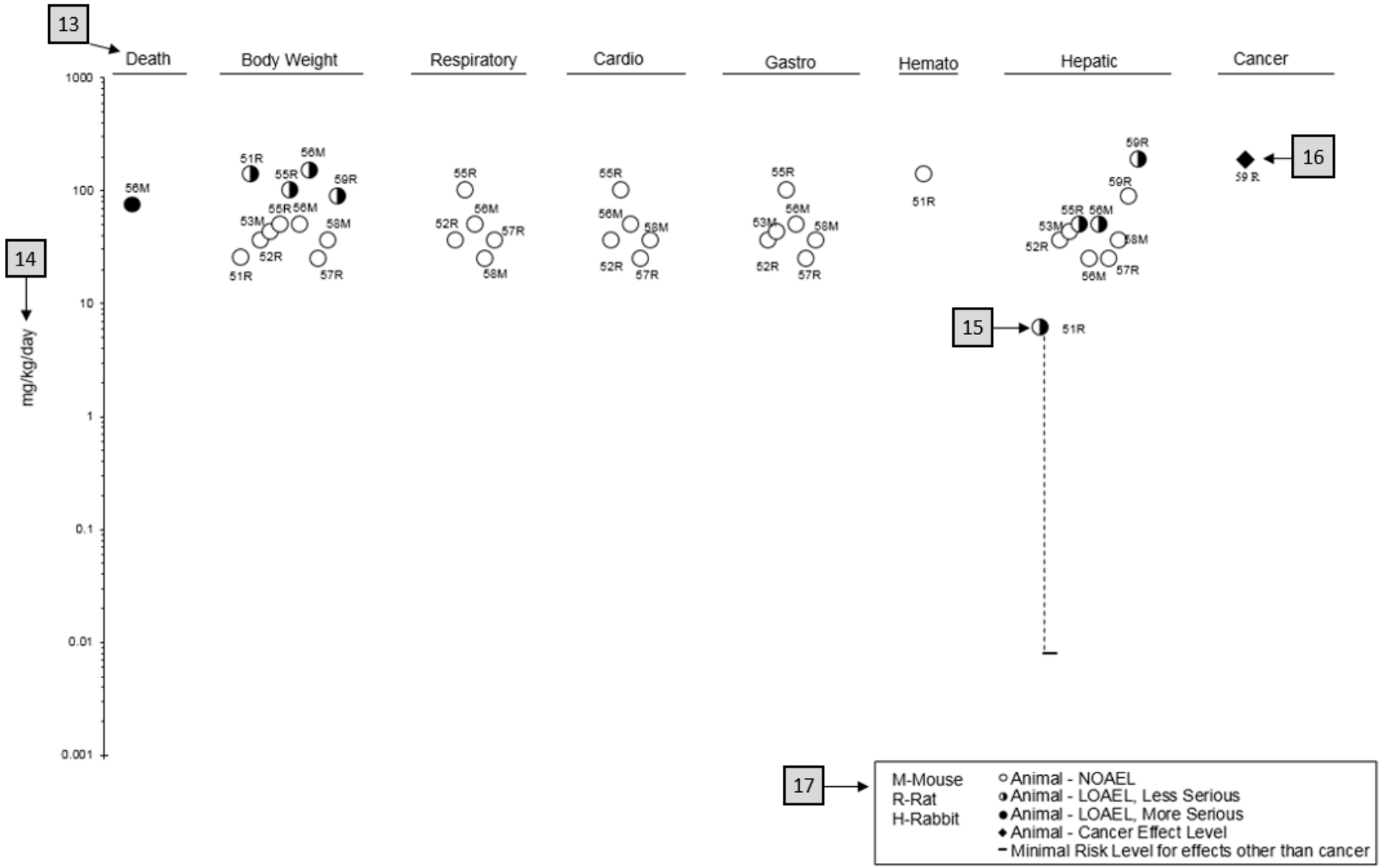
Figure key[a] (3)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0,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

Case Studies in Environmental Medicine are self-instructional publications designed to increase primary health care providers' knowledge of a hazardous substance in the environment and to aid in the evaluation of potentially exposed patients (see https://www.atsdr.cdc.gov/csem/csem.html).

Managing Hazardous Materials Incidents is a set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.asp).

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: https://www.cdc.gov/nceh/.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: https://www.niehs.nih.gov/.

Clinical Resources (Publicly Available Information)

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: http://www.acoem.org/.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at http://pehsu.net/findhelp.html.

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

APPENDIX F. GLOSSARY

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

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

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

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

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

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

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

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

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

Carcinogen—A chemical capable of inducing cancer.

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

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

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

Ceiling Value—A concentration that must not be exceeded.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Toxics Release Inventory (TRI)—The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

Xenobiotic—Any substance that is foreign to the biological system.

APPENDIX G. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	American Association of Poison Control Centers
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ACMT	American College of Medical Toxicology
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AIC	Akaike's information criterion
AIHA	American Industrial Hygiene Association
ALT	alanine aminotransferase
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BCF	bioconcentration factor
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
C	centigrade
CAA	Clean Air Act
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CDR	Chemical Data Reporting
CEL	cancer effect level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
cm	centimeter
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
ERPG	emergency response planning guidelines
F	Fahrenheit
F1	first-filial generation
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act

FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GGT	γ-glutamyl transferase
GRAS	generally recognized as safe
HEC	human equivalent concentration
HED	human equivalent dose
HHS	Department of Health and Human Services
HPLC	high-performance liquid chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Level of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
MRL	Minimal Risk Level
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
Mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NCEH	National Center for Environmental Health
ND	not detected
ng	nanogram
NHANES	National Health and Nutrition Examination Survey

NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEHSU	Pediatric Environmental Health Specialty Unit
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure level/limit
REL-C	recommended exposure level-ceiling value
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
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